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Population Reports

Oral Contraceptives

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OCs—Update on Usage, Safety, and Side Effects

Summary. After nearly two decades of use, oral contraceptives (OCs) are the most popular reversible method of contraception in the world today. According to marketing statistics gathered from at least 31 countries, about 325 million cycles of oral contraceptives were sold in 1977. This quantity would supply 25 million women for one year, of whom about 21 million are in developed countries and 4 million in developing countries. Although sales are leveling off or declining somewhat in Western Europe and the United States, where use rates now range up to 40 percent of women aged 15–44, sales are increasing rapidly in Asia and Latin America.

At the same time, national family planning programs in developing countries provide oral contraceptives on a free or subsidized basis to about 9 million women (excluding the People's Republic of China). The United States Agency for International Development (USAID) delivered close to 100 million cycles annually to these countries over the last five years. Other governments and United Nations agencies also provide supplies for national programs. It is estimated that, including 10–15 million users in the People's Republic of China, about 54 million women throughout the world were using oral contraceptives in 1977, an increase of 4 million over the estimate published in **Population Reports** in 1974.

Circulatory System Disease

With respect to the safety of oral contraceptives, data from three major cohort studies in Britain and the United States throw new light on the relationships between OC use and circulatory system disease. A study of 46,000 British women by the Royal College of General Practitioners found that:

- OC users experienced higher death rates from circulatory system disease—25.8 per 100,000 woman-years of observation—than did women who had never used orals—5.5 per 100,000 woman-years. These rates are averages including women with conditions conducive to circulatory system disease as well as women with no such conditions.

- OC users faced a greater range of circulatory system diseases than was originally suspected, including arterial as well as venous disorders. In addition to myocardial infarction, pulmonary embolism, and cerebral hemorrhage, women in this study experienced subarachnoid hemorrhage, malignant hypertension, cardiomyopathy, and mesenteric-artery thrombosis.

- Women who used OCs for five years or more faced a tenfold greater risk of death from circulatory disease than women who never used the pill. Even after discontinuing, women who had used the pill faced slightly higher risks, especially of subarachnoid hemorrhage.

- Most important for individuals and for family planning programs, these risks do not apply to all women equally. Women over 35 and women who smoke face by far the greatest hazards. Death rates for OC users aged 35–44 were 42.6 per 100,000 woman-years and for OC users who smoke, 39.5 per 100,000 woman-years, compared with less than 9 for OC users under 35 and about 14 for OC users who do not smoke.

These findings from the Royal College study are generally confirmed by other published British data from the Oxford/Family Planning Association study and by data now becoming available from the United States study in Walnut Creek, California. All three studies highlight the previously suspected but not proved effect of smoking, which may not merely add to but in some diseases multiply the risk associated with OC use. It is also becoming clear that other factors predisposing to the development of circulatory disease—hypertension, high cholesterol levels, diabetes,

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and obesity—play important roles in mortality among OC users.

A key question not answered by any of the studies is the extent of risk for women under 35 who do not smoke and who have no other conditions predisposing them to develop circulatory system disease. Despite the fact that, in the largest study, 46,000 women had a cumulative experience of some 200,000 woman-years, there were so few deaths among the younger, nonsmoking women (one, at age 32) that it is not possible to determine at acceptable levels of statistical significance what residual risk of oral contraceptive use remains for these women. Although an increased risk probably exists, it is very small.

To complicate the issue further, analysis of circulatory system disease death rates in countries where OC use is high does not show the changes that would be expected if the use of OCs in fact produced a fivefold increase in deaths among all users. For example, in the United States, England and Wales, and Denmark, the trend of all circulatory disease death rates has been downward, with the exception of diseases of the veins, for women of all ages, even in the face of increases in OC use.

Further, in a 21-country analysis, WHO researchers found that improving death rate trends for women aged 35–44 were associated with trends of increasing OC usage. While national mortality data by their very nature cannot provide conclusive evidence of slight risks in oral contraceptive use, analyses of these trends do reinforce the other indications that any increased risk from OC use is relatively small and is largely, if not entirely, limited to specific subgroups of women—those over 35, those who smoke, and those with other conditions predisposing them to circulatory system disease.

With regard to cancer, no definitive new data are available, but this in itself is reassuring. The fact that cancers have long latent periods has been used to argue against reaching any conclusion prematurely. With oral contraceptive use now in its second decade, that argument is losing some of its force.

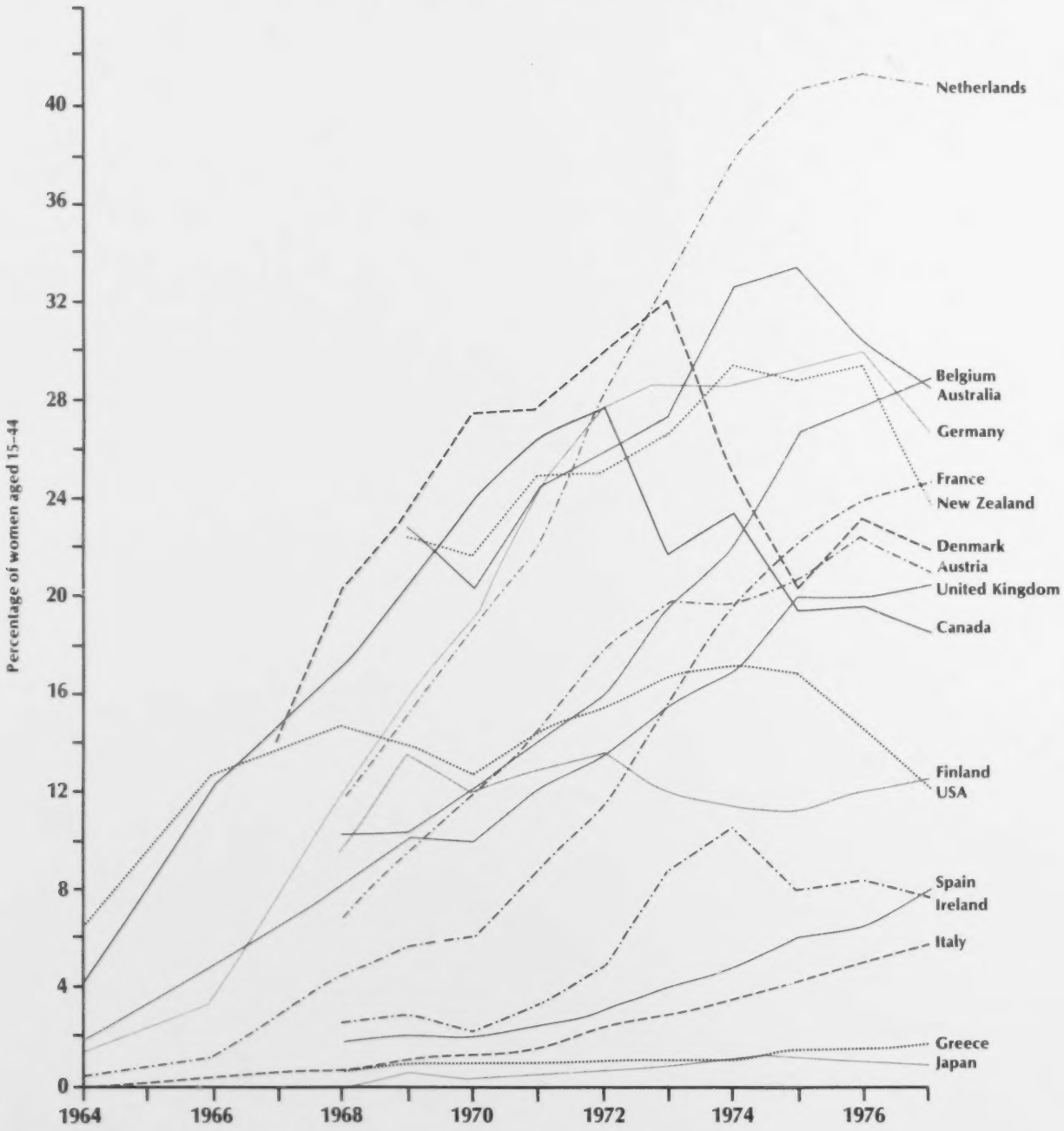
Investigations of other possible side effects have revealed no substantial new risks associated with OC use, and, in fact, some fears—particularly over adverse effects on subsequent fertility and on offspring conceived after pill use—have been eased by recent reports. Unsuspected benefits—a possible protective effect against ovarian cancer and an apparent reduction in rheumatoid arthritis—have been noted.

Virtually all the data on serious side effects of oral contraceptives come from developed countries, where circulatory disease and the factors predisposing women to it are common, perhaps affecting as much as one-third of the female population of reproductive age. In these countries, the continuing usage and popularity of oral contraceptives underline the need to identify and inform those women who face special risks so that they can make knowledgeable choices of their method of family planning and, in the interests of their long-term health, stop smoking and possibly modify their diet and lifestyles. For older couples or those whose families are complete, voluntary sterilization provides an acceptably safe and increasingly popular alternative.

What are the implications of these findings for developing countries? First, it should be emphasized that US and British findings cannot automatically be applied to women in developing country settings. In the developing world, circulatory system disease is rare, cholesterol levels are low, and few women smoke, so it may well be that OC use poses no serious threat of circulatory disease in most developing countries. Second, there is increasing need, as OC use in these areas expands, to determine what the various hazards may be in developing countries and which women face the greatest risk. Should an increased risk be demonstrated, it might then be relatively easy, by self-screening or program check lists at the village level, to encourage sterilization or use of other methods by high-risk women.

Overall, the risks of using any contraceptive method are far outweighed in the developing countries by the much greater risks of pregnancy and childbirth. In Bangladesh, for instance, where use of contraceptives is negligible, almost 200 women per 100,000 in each 5-year age group can be expected to die in childbirth. This should be compared with about 10 to 20 deaths per 100,000 associated with the use of orals by Bangladeshi women under age 40. Even in developing countries where maternal mortality is lower than in Bangladesh, OCs are much safer than childbirth at all ages below 40. Under these circumstances, the continued increase in OC use in the developing world and the

Figure 1. Minimum Percentage of Women Aged 15-44 Supplied with Oral Contraceptives through Commercial Channels in 17 Developed Countries, 1964-1977



Source: IMS International/America, Ltd., studies prepared for the Population Information Program, 1977 and 1978 (81, 82); Gram (67) (Denmark only)

spread of community-based distribution systems (described in **Population Reports** J-19) are well justified from a public health point of view, contributing as they do not only to lower birth rates but also to improved maternal health and survival.

COMMERCIAL SALES

Combined oral contraceptives—consisting of an estrogen and a progestin component—were first marketed in June 1960 in the United States. Within five years, purchases of OCs for prescription sales by US pharmacies had reached 65 million cycles. In other developed countries sales of oral contraceptives began somewhat later but increased with comparable or greater rapidity. Today these sales constitute the major source of oral contraceptive supplies for women in developed countries and an increasingly important source of supply in developing countries (see **Population Reports** A-1, April 1974).

Purchases of oral contraceptives (and other prescription drugs) by pharmacies are audited regularly by IMS, Ltd. Data are compiled from invoices gathered from a sample of pharmacies or, in a few cases, from wholesalers and prescribing physicians in major pharmaceutical marketing areas. The sample ranges from about one percent to 10 percent of the total number of pharmacies in each country. The pharmacies sampled are chosen as representative of the range of shop size, based on total store sales volume, within each region. Purchases by hospitals and family planning clinics, donations, and free samples are excluded, as are purchases by other outlets. The latter may account for a portion of sales in countries where a prescription is not required by law. All pharmacy purchases are included, whether or not customers are required to have prescriptions.

Total pharmacy purchases of oral contraceptives in these major market areas in the developed and developing countries amounted in 1977 to nearly 325 million cycles, representing some 25 million woman-years of contraception. This is an increase of about 5 million users since 1972 (see **Population Reports** A-1, April 1974). Generally, commercial sales in Western Europe and the English-speaking world reached a peak in 1975 and declined somewhat in 1976 and 1977, with the biggest declines occurring in the United States during 1976 and 1977 and in the Federal Republic of Germany during 1977 (see Table 1).

In the developing countries, sales continue to grow, especially in Brazil, where more than 2 million women are now buying oral contraceptives (see Table 1). Commercial sales of OCs in the developing world account for only about 56 million cycles, less than one-fifth as many as in developed countries. Since 1970, however, sales have increased by an average of nearly 6 million cycles annually, with the greatest increase between 1972 and 1973. Asian sales have tripled since 1972 and in Latin America, starting from a larger base, they have more than doubled. Nevertheless, even in Brazil and Puerto Rico, where usage is highest, fewer than 10 percent of the women of reproductive age are purchasing oral contraceptives regularly (see Table 2).

In the developed countries, despite declining sales in the last two years, oral contraceptives are still widely sold to women who can afford prices ranging upward from $1.50 (US) per month. In 12 of the 18 developed countries for which IMS has current data—Australia, Austria, Belgium, Canada, Finland, Federal Republic of Germany, France, the Netherlands, New Zealand, Portugal, the United States, and the United Kingdom—more than 10 percent of all women aged 15-44 are buying orals (see Figure 1). In the United States enough oral contraceptives were sold to pharmacies in 1977 to provide 12.2 percent of all women aged 15-44 with a full year's supply. The Netherlands has the highest proportion of OC users, over 40 percent.

Other data, some from the National Survey of Family Growth, confirm relatively high rates of oral contraceptive use in the United States. In 1976, 22.3 percent of married women of reproductive age (MWRA) were using oral contraceptives, down slightly from 25.1 percent, recorded in 1973 (60). While orals are still the choice of younger women and women who intend to have more children, sterilization is increasingly chosen by older couples. By 1976, 28.3 percent of couples where the wives were aged 15-44 reported husband or wife sterilized, 19.3 percent for contraceptive reasons. Among couples where the wives were aged 30-44, 28.4 had chosen sterilization for contraceptive reasons, with an equal proportion of husbands and wives sterilized. Thus the popularity of voluntary sterilization now rivals that of oral contraceptives (221).

In organized US family planning programs, which serve about 3 million women, the proportion of clients using pills is very high, 67.2 percent, while that choosing sterilization is quite low, probably reflecting referrals of sterilization clients to other services. The percentage of these clinic-served women using orals has fallen slightly from 70.3 percent in 1970 (200).

The trend in the United States toward selection of formulations with lower estrogen content is continuing, according to IMS data (see Table 3). Combination oral contraceptives with 50 μg of estrogen—which constituted less than 10 percent of the market in 1967—increased their share to more than 50 percent by 1977. Moreover, since 1972 formulations with even less than 50 μg of estrogen have been approved, and they now account for nearly 18 percent of the market. OCs with 100 or more μg of estrogen constitute less than 20 percent of prescription sales, but the 100 μg and 80 μg formulations, while falling from 43.6 percent of the market in 1973, are still the choice of one-quarter of US pill users. The continued use of these formulations may be explained by some women's need for more estrogen to prevent breakthrough bleeding or by preferences for familiar and satisfactory brands.

Oral contraceptive use is high in a number of developed countries not included in the IMS audit. For example, in Denmark in 1976, 1977, and the first half of 1978, there were approximately 240,000 women using oral contraceptives, or 23 percent of women aged 15-44 (7); in Sweden an average of about 6 million cycles was sold in 1976 and 1977 (48), representing about 460,000 women or 28 percent of women aged 15-44; and in Hungary an estimated 500,000 women were using orals in 1976, or about 20 percent of all women aged 17-49 (101, 102).

Table 1. Retail Pharmacy Purchases of Oral Contraceptives in Selected Areas, by Country and Year, 1970–1977
(in thousands of cycles)

	1970	1971	1972	1973	1974	1975	1976	1977
DEVELOPED AREAS								
Australia	6,815.7	8,191.3	8,976.5	9,813.8	11,983.2	12,561.4	11,667.8	11,056.7
Austria	2,174.1	2,671.2	3,332.0	3,743.3	3,738.1	3,956.2	4,316.8	4,130.3
Belgium	2,996.0	3,464.6	3,909.8	4,957.5	5,563.9	6,796.5	7,141.0	7,471.0
Canada	14,012.0	15,889.0	17,117.0	13,884.5	15,315.0	12,952.1	13,413.5	13,024.0
Finland	1,610.7	1,782.2	1,865.9	1,589.0	1,527.9	1,507.0	1,629.9	1,703.9
France	8,231.0	11,833.9	15,299.0	21,495.9	27,221.1	31,133.9	33,796.4	35,088.7
Germany, Fed. Rep.	29,369.9	37,879.1	42,901.1	45,746.0	45,833.5	47,178.6	48,950.0	44,220.2
Greece	226.9	277.1	286.9	271.0	266.9	364.0	367.8	383.3
Ireland*	151.5	228.8	334.4	657.8	805.6	623.5	671.6	637.1
Italy	1,808.8	2,231.2	3,677.4	4,268.2	5,334.2	6,431.1	7,625.6	8,438.6
Japan*	1,042.6	1,368.2	1,911.9	2,804.4	4,450.2	4,135.7	3,708.7	3,180.3
Netherlands	6,518.0	7,760.0	10,149.6	11,998.5	13,959.9	15,204.6	15,693.9	15,749.2
New Zealand	1,593.6	1,896.6	1,949.8	2,082.3	2,381.6	2,354.5	2,460.9	2,052.5
Portugal						3,040.9	3,752.0	3,981.0
South Africa						2,414.0	2,246.6	2,026.5
Spain	1,823.4	2,285.0	2,760.0	3,753.8	4,447.4	5,756.8	6,146.8	7,539.3
United Kingdom	13,824.7	16,997.9	18,948.2	21,790.5	23,812.5	28,163.6	28,494.2	29,492.9
United States	70,655.3	81,203.7	89,147.2	98,327.0	102,761.0	102,790.0	90,690.0	77,589.0**
Subtotal	162,854.2	195,959.8	222,566.7	247,183.5	269,402.0	287,364.4	282,773.5	267,764.5
DEVELOPING AREAS								
Asia								
Indonesia						792.3	931.2	1,028.1
Iran			596.8	615.5	639.5	866.1	1,199.0	1,529.4
Pakistan						166.8	216.9	218.6
Philippines	982.9	755.2	623.0	745.6	798.2	697.7	697.9	740.0
Saudi Arabia						560.9	328.4	473.2
Turkey	932.1	1,349.5	1,484.4	1,958.1	1,876.5	2,461.4	3,038.5	4,144.1
Subtotal	1,915.0	2,104.7	2,704.2	3,319.2	3,314.2	5,545.2	6,411.9	8,133.4
Latin America								
Argentina	3,406.0	3,514.3	3,924.3	4,306.4	4,297.7	3,209.1	3,863.4	3,388.2
Brazil	6,895.0	9,314.3	10,383.2	17,966.3	22,490.8	26,207.4	24,320.6	28,577.8
Central America			1,012.8	1,112.8	1,103.1	1,097.7	1,249.1	1,192.8
Colombia	1,105.0	1,404.2	1,641.5	2,048.3	2,417.2	2,794.3	3,064.1	3,328.3
Ecuador						470.1	532.8	533.6
Mexico	2,810.0	2,715.8	3,628.4	5,244.6	5,974.4	6,176.8	6,373.5	7,244.3
Peru	376.0	497.6	680.3	867.0	1,203.6	986.0	1,171.1	1,218.5
Puerto Rico	233.0	311.0	427.0	449.9	809.0	840.3	715.2	885.8
Venezuela	553.0	716.1	828.4	1,203.7	1,361.9	1,512.7	1,764.1	2,000.3
Subtotal	15,378.0	18,473.3	22,525.9	33,199.0	39,657.7	43,294.4	43,053.9	48,369.6
TOTAL	180,147.2	216,537.8	247,796.8	283,701.7	312,373.9	336,204.0	332,239.3	324,267.5

*Products licensed for therapeutic, not contraceptive purposes
**In the 12 months ending June 1978, 71,895

Note: These figures do not include subsidized programs, samples, or sales to hospitals or family planning clinics.

Source: IMS International/America, Ltd., studies prepared for the Population Information Program, 1977 and 1978 (81, 82)

Table 2. Minimum Percentage of Women Aged 15–44 Supplied with Oral Contraceptives through Commercial Channels in Selected Areas, 1970–1977

	1970	1971	1972	1973	1974	1975	1976	1977
DEVELOPED AREAS								
Australia	20.2	24.2	25.6	27.2	32.5	33.4	30.3	28.0
Austria	11.8	14.4	17.9	19.8	19.6	20.7	22.3	21.0
Belgium	12.1	14.0	15.6	19.5	21.8	26.5	27.6	28.7
Canada	23.9	26.4	27.7	21.7	23.4	19.4	19.6	18.7
Denmark*	27.5	27.6	29.9	32.1	24.9	20.3	23.2	22.2
Finland	11.9	13.1	13.6	11.9	11.4	11.2	12.0	12.5
France	6.1	8.8	11.3	15.6	19.6	22.2	23.9	24.6
Germany, Fed. Rep.	18.9	24.4	27.6	28.7	28.6	29.3	30.0	26.8
Greece	0.9	1.0	1.1	1.1	1.1	1.5	1.5	1.6
Ireland	2.2	3.2	4.8	8.7	10.5	7.9	8.3	7.7
Italy	1.2	1.5	2.4	2.9	3.6	4.3	5.1	5.6
Japan	0.3	0.4	0.6	0.8	1.3	1.2	1.1	0.9
Netherlands	18.6	21.8	28.1	32.8	37.7	40.5	41.2	40.8
New Zealand	21.5	24.9	25.0	26.6	29.7	28.7	29.3	23.9
Portugal					0.7	12.3	15.0	15.8
South Africa						3.4	3.1	2.7
Spain	1.9	2.4	3.0	4.0	4.7	6.1	6.4	7.8
United Kingdom	9.9	12.1	13.4	15.5	16.9	19.8	19.8	20.3
United States	12.7	14.4	15.4	16.7	17.1	16.8	14.5	12.2
DEVELOPING AREAS								
Asia								
Indonesia						0.2	0.2	0.2
Iran			0.8	0.8	0.8	1.0	1.3	1.6
Pakistan							0.1	0.1
Philippines	1.0	1.3	0.6	0.7	0.7	0.6	0.6	0.6
Saudi Arabia						0.3	1.3	1.9
Turkey	1.0	1.4	1.5	1.9	1.8	2.3	2.8	3.7
Latin America								
Argentina	4.9	5.0	5.6	6.2	6.1	4.5	5.4	4.7
Brazil	2.7	3.5	3.8	6.2	7.5	8.5	7.7	8.7
Colombia	1.9	2.4	2.7	3.2	3.6	4.0	4.2	4.4
Ecuador						2.5	2.7	2.6
Mexico	2.1	2.0	2.5	3.6	4.0	4.0	3.9	4.3
Peru	1.0	1.3	1.8	2.2	3.0	2.3	2.7	2.7
Puerto Rico	2.9	3.7	5.0	5.4	9.5	9.6	8.0	9.3
Venezuela	2.0	2.6	2.9	3.9	4.3	4.6	5.1	5.6

Note: These percentages were calculated from the data in Table 2 as follows:
1) Pharmacy sales of oral contraceptives were divided by 13 to give the maximum number of women taking oral contraceptives for one full year or woman-years of use.
2) Woman-years were divided by the female population aged 15–44 × 100 to give the minimum percentage of women aged 15–44 buying oral contraceptives in sufficient quantity for one year of use.

These figures represent the minimum number of users because the woman-years concept counts, for example, two women using orals for 6 months apiece as one woman-year. On the other hand, pharmacy purchases from wholesalers include supplies in inventory and thus may overcount actual users during a period of inventory build-up. No attempt is made in these data to account for nonfertile women or women not married, not at risk of pregnancy, or already pregnant.

Source: IMS International/America, Ltd., studies prepared for the Population Information Program, 1977 and 1978 (81, 82)
*Anderson (7), Gram (67)

FAMILY PLANNING PROGRAM DISTRIBUTION

Unlike the developed countries, where commercial sales account for most of the contraceptives used, in the developing countries organized family planning programs play the major role in supplying women with oral contraceptives. Since 1967 the US Agency for International Development (USAID) has been the most important source of supply for developing country programs, in both the public and private sectors (see Table 4 and Figure 2). USAID supplies have increased from less than 4 million cycles in 1968 to close to an estimated 105 million in 1978. Since 1974, when USAID shipments more than doubled, from 40 million to 103 million, yearly deliveries to some 65 countries have averaged about 97 million cycles. Countries now receiving the largest quantities are Morocco, Bangladesh, Indonesia, the Philippines, and Thailand. USAID pays about $.18 (US) a cycle, including shipping. Supplies also go to private voluntary agencies like the International Planned Parenthood Federation for use in their programs.

Another government that has made oral contraceptives available to developing countries is Sweden. Through its International Development Authority (SIDA), Sweden provided or acted as a purchasing agent for some 40 million cycles between 1967 and 1973 (see **Population Reports** A-1, p. A20) and another 13 million during 1974-1977. Swedish donations in 1977 amounted to about 4 million cycles for Kenya, Sri Lanka and Viet-Nam. In 1978 SIDA plans to ship 50,000 cycles to Sri Lanka only (see Table 5). The United Nations Fund for Population Activities (UNFPA) will continue to provide contraceptives to most of the other countries.

As a source of support for national government population programs, including provision of contraceptive supplies, UNFPA is playing an increasing role. UNFPA funding for all contraceptive supplies totalled approximately $13 million between 1969 and 1976, with $3.4 million expended in 1977 and $5.3 million budgeted in 1978. Oral contraceptives may represent roughly 60 percent of these figures at an average cost per cycle, including shipping, of $.25 (US). UNFPA has provided raw materials for the manufacture of oral contraceptives to Egypt, India, and Cuba. Within the UN system about 80 percent of the contraceptives funded by UNFPA are purchased and delivered by the UN Children's Fund (UNICEF) and 20 percent by the World Health Organization (WHO). According to USAID data on oral contraceptive deliveries received during 1977, some 2 million cycles from UN agencies reached Bangladesh; 1.3 million, Thailand; 1 million, Costa Rica; 708,000, Colombia; and smaller amounts, Tunisia, El Salvador, the Dominican Republic, Haiti, and Paraguay.

Other donors who provide quantities of oral contraceptives—often brands or formulations which USAID does not provide—include the International Planned Parenthood Federation, the Pathfinder Fund, Family Planning International Assistance, and other governments. The total supply now provided as development assistance is probably in the neighborhood of 120 million cycles, or about double the amount sold through commercial channels in developing countries.

Table 3. Oral Contraceptives Sold in the United States, by Progestin and Estrogen Content, 1963-1978

Content (in mg)	Dollar Sales Volume as Percent of Market								
	1963	1967	1972	1973	1974	1975	1976	1977	1978*
Progestins									
Combination									
10.0	21.2	3.5	2.0	0.4	0.4	0.4	0.3	0.3	0.2
5.0	78.8	4.5		1.1	0.8	0.6	0.4	0.4	0.3
2.5	0.0	12.0	14.0	5.9	5.4	4.8	4.2	3.8	3.3
2.0	0.0	28.0		7.2	5.8	4.5	4.2	3.8	2.8
1.5				0.1	0.8	1.3	2.0	2.3	2.4
1.0-1.5	0.0	30.0	77.0						
1.0				54.7	56.2	56.4	57.3	57.9	57.4
0.5				23.4	24.3	24.9	22.7	21.5	22.3
0.4				0.0	0.0	0.0	0.2	0.2	0.3
0.35				0.3	0.2	0.2	0.2	0.1	0.1
0.3				0.0	0.0	1.5	6.9	9.5	10.7
0.075				0.0	0.2	0.1	0.0	1.0	1.0
Sequentials (all)	0.0	22.0	7.0	6.8	5.8	5.4	1.6	0.0	0.0
Total	100.0	100.0	100.0	100.0	100.0	100.0	100.0	100.0	100.0
Estrogens									
> 0.100	13.9	17.7	9.2	0.3	0.2	0.2	0.1	0.2	0.1
0.100	2.3	56.0	21.8	27.4	25.3	23.2	19.1	16.6	14.1
0.080	0.0	5.8	15.5	16.2	16.8	16.4	14.9	13.2	12.5
0.075	74.6	10.1	1.8	1.1	0.8	0.6	0.4	0.4	0.3
0.060	9.2	0.7	0.4	0.2	0.2	0.2	0.1	0.1	0.1
0.050	0.0	9.7	51.3	53.1	54.4	53.9	53.4	53.6	54.5
0.035				0.0	0.0	1.3	1.5	2.9	4.2
0.030				0.1	0.8	2.8	8.9	11.8	13.1
0.020				1.3	1.1	1.1	1.3	1.0	0.9
0**				0.3	0.4	0.3	0.2	0.2	0.2
Total	100.0	100.0	100.0	100.0	100.0	100.0	100.0	100.0	100.0

*12 months ending June 1978
**Progestin-only minipill

Source: IMS America, Ltd., study conducted for the Population Information Program, 1977 and 1978 (81)

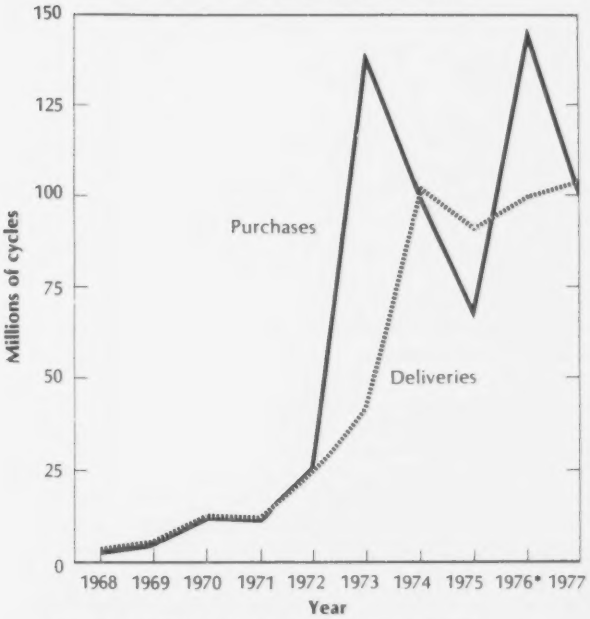
Table 4. Deliveries of Oral Contraceptives (in thousands of cycles) Financed by the United States Agency for International Development by Calendar Year and Area, 1967–1978

	1967	1968	1969	1970	1971	1972	1973	1974	1975	1976	1977	Est. 1978	Total
AFRICA													
Botswana	—	—	—	—	—	100	—	50	25	—	2	22	199
Ethiopia	—	—	29	—	5	—	30	—	313	—	—	—	377
Ghana	—	40	83	87	407	79	324	1,235	1,090	1,749	—	90	5,184
Kenya	—	103	215	20	49	81	179	253	100	—	—	—	1,000
Lesotho	—	—	—	—	—	—	16	50	6	20	—	—	92
Liberia	—	—	—	—	30	30	60	2	—	107	—	20	249
Mauritius	—	—	—	—	50	—	—	5	5	—	—	—	60
Morocco	—	—	30	40	160	200	987	2,300	703	700	5,011	5,000	15,131
Nigeria	—	—	85	15	120	50	167	25	160	—	6	—	628
Sierra Leone	—	—	10	—	10	5	2	61	3	15	—	22	128
Sudan	—	—	—	—	—	—	—	14	85	—	102	20	221
Swaziland	—	—	—	—	—	—	—	158	—	—	—	—	158
Seychelles	—	—	—	—	—	—	3	62	8	—	—	—	73
Tanzania	—	—	50	—	40	55	80	52	315	485	1,801	1,844	4,722
Tunisia	—	180	92	64	12	220	72	271	160	930	670	720	3,391
Uganda	—	—	—	10	20	5	—	50	16	150	—	30	281
Zaire	—	—	—	—	—	—	27	142	25	20	150	—	364
Zambia	—	—	—	—	—	—	5	50	226	20	—	—	301
Other (6)*	—	22	19	—	34	25	10	24	10	5	—	41	190
Subtotal	—	345	613	236	937	850	1,962	4,804	3,250	4,201	7,742	7,809	32,749
ASIA													
Afghanistan	—	60	40	100	170	—	—	240	400	27	—	200	1,237
Bangladesh	—	—	—	—	—	175	20	9,087	7,540	8,655	10,570	18,503	54,550
Egypt	—	—	—	—	—	—	—	1,200	—	—	—	—	1,200
Hong Kong	—	15	220	—	300	250	150	50	—	—	—	—	985
India	30	970	470	—	—	—	—	—	—	—	—	—	1,470
Indonesia	—	261	90	1,100	2,100	5,640	15,636	18,807	29,188	30,800	59,160	36,216	198,998
Iran	—	—	—	—	—	—	—	103	—	10	—	50	163
Jordan	—	—	—	—	—	60	—	—	—	—	—	—	60
Korea, South	—	—	—	—	—	—	—	3,000	2,300	—	—	—	5,300
Laos	—	—	3	—	4	20	350	434	—	—	—	—	811
Malaysia	—	—	300	193	340	395	390	523	205	65	80	—	2,491
Nepal	—	155	100	100	5	44	446	906	575	3,300	—	—	5,631
Pakistan	—	26	—	400	350	395	40	4,676	10,123	12,568	—	—	28,578
Philippines	—	165	375	1,900	1,867	6,012	6,148	26,773	11,780	500	1,435	10,601	67,556
Singapore	—	436	—	—	—	—	—	—	—	—	—	—	436
Sri Lanka	—	37	30	35	50	100	25	184	50	—	—	—	511
Taiwan	—	50	220	580	500	1,942	935	1,620	—	135	—	—	5,982
Thailand	—	500	50	4,600	2,320	3,130	7,150	8,618	8,454	16,691	2,500	4,411	58,424
Vietnam	—	89	128	—	78	435	70	1,475	176	—	—	—	2,451
Other(7)*	—	6	—	—	—	1	—	144	3	28	30	31	243
Subtotal	30	2,770	2,026	9,008	8,084	18,599	31,360	77,840	70,794	72,779	73,775	70,012	437,077
LATIN AMERICA													
Barbados	—	17	36	60	200	—	70	74	—	—	—	—	457
Chile	—	—	80	800	—	500	389	1,863	1,360	600	816	—	6,408
Colombia	—	—	50	120	80	322	1,347	1,855	2,278	1,550	—	—	7,602
Costa Rica	—	35	—	225	150	159	322	335	800	400	—	504	2,930
Domin. Rep.	90	100	106	—	200	226	—	200	5	50	—	75	1,052
Ecuador	—	15	40	59	48	394	25	—	41	—	—	—	622
El Salvador	—	50	90	251	385	120	100	652	150	1,701	1,015	1,401	5,915
Mexico	—	—	—	—	—	—	—	—	—	—	—	10,502	10,502
Guatemala	—	110	100	120	250	200	349	415	600	380	—	—	2,524
Haiti	—	—	—	—	—	—	—	—	—	—	—	1,333	1,333
Honduras	—	15	75	77	169	310	84	461	640	1,295	—	356	3,482
Jamaica	—	195	196	105	5	41	183	701	400	524	550	397	3,297
Nicaragua	—	50	—	—	123	90	110	612	320	160	1,337	1,000	3,802
Panama	—	5	—	105	—	52	344	670	115	—	600	—	1,891
Paraguay	—	7	—	4	25	89	152	309	335	205	581	461	2,168
Peru	—	—	—	—	—	—	—	—	—	—	—	208	208
Uruguay	—	—	—	40	—	5	—	10	24	20	50	50	199
Venezuela	—	10	40	160	390	300	1,020	1,268	1,930	950	—	413	6,481
Other (17)*	—	14	61	101	148	64	159	143	323	44	2	25	1,084
Subtotal	90	623	874	2,227	2,173	2,872	4,654	9,568	9,321	7,879	4,951	16,725	61,957
Country NA	—	152	896	800	48	689	2,889	10,938	5,327	14,941	5,947	10,537	53,164
TOTAL	120	3,890	4,409	12,271	11,242	23,010	40,865	103,150	88,692	99,800	92,415	105,083	584,947

*Other—Designates countries with less than 50,000 cycles in any year, i.e., **Africa**: Burundi, Benin, Gambia, Rwanda, Senegal, Togo; **Asia**: Ryukyu Islands, Tonga, Khmer Rep., Lebanon, Iraq, Syrian Arab Rep., Cyprus; **Latin America**: Argentina, Antigua, Aruba, Bolivia, Dominica, Grenada, Guyana, Mauritius, Montserrat, Netherlands Antilles, Peru, St. Kitts, St. Lucia, St. Vincent, Surinam, Trinidad, Windward Islands.

Source: USAID, Office of Population (203, 204)

Figure 2. Purchases and Deliveries of Oral Contraceptives Financed by the United States Agency for International Development, by Fiscal Year for Purchases and by Calendar Year for Deliveries, 1968–1977



*Fiscal year 1976 includes July through September 1976.

Source: USAID, Office of Population (203, 204)

ESTIMATING USAGE

Counting, calculating, or estimating oral contraceptive usage in developing countries is difficult by any method. Although family planning program statistics are improving in most countries, they do not include commercial usage, and they often do not include programs sponsored by nongovernmental agencies. Table 6 presents and compares data on 1977 usage gathered by the Population Council and by USAID. In most cases, the Population Council figures are for January 1977, the USAID figures for October–November–December 1977. In countries with rapidly advancing programs, a year's time may make some difference, but other discrepancies between the estimates remain—in service program tallies, in commercial sales estimates, and even in the estimated numbers of married women of reproductive age that are used to calculate use rates.

Nonetheless, it is clear that in Africa only four countries report OC usage rates near or above 5 percent of married women of reproductive age: Egypt, reporting about 10 percent; Mauritius, with a high rate among developing countries of 29.2 percent; and Morocco and Tunisia, each with about 5 percent.

In Asia, at least nine countries appear to have usage rates higher than 5 percent: Hong Kong with 28 percent; Iran, reporting 21 percent, and Malaysia, reporting 27 percent (both figures that may be questionable); Singapore, Indonesia, and Thailand, between 12 and 17 percent; and Fiji, the Philippines, and Taiwan, between 5 and 10 percent.

In the Western Hemisphere also, at least nine developing countries may now have more than 5 percent of married women of reproductive age using orals: Costa Rica and Jamaica, both well over 20 percent; Colombia, the Dominican Republic, Nicaragua, Panama, and Paraguay, around 15 percent; and El Salvador and Mexico, between 5 and 10 percent.

Family planning service statistics such as these often reflect hopes as well as performance. Alternate sources of countrywide data now available are the various World Fertility Surveys, in which a representative sample of women of reproductive age is asked extensive questions on socioeconomic, demographic, fertility, and contraceptive status. Data from 11 countries have been released (see Table 7). These confirm oral contraceptive prevalence rates of more than 10 percent in Malaysia, Thailand, Colombia, Costa Rica, and Panama. Only Costa Rica is over 20 percent. These surveys were taken in 1974, 1975, and 1976, however, and some increases in usage would be likely in the years since.

Most of the developing countries which show high acceptance of oral contraceptives are those in which community-based or commercial distribution programs have been established. OCs are distributed in these countries by paramedical personnel, for example, midwives (as in Thailand and Malaysia), by community workers and village leaders (as in Colombia and Indonesia), or at subsidized rates through pharmacies or local shops and bazaars (as in Tunisia, Colombia, and Sri Lanka). In countries where physicians are in general scarce and in rural areas almost impossible to find, oral contraceptive use cannot be expanded except through nonmedical, nonclinical distribution systems (see **Population Reports** J-19, Community Based and Commercial Contraceptive Distribution: an Inventory and Appraisal, March 1978).

Not included in these tables are data on oral contraceptive use in the People's Republic of China. No Chinese data have been published either on production of steroid contraceptives or on nationwide use. Figures from selected communes given to visitors show OC use rates ranging

Table 5. Deliveries of Oral Contraceptives Financed by the Swedish International Development Authority, by Calendar Year and Area, 1974–1977
(in thousands of cycles)

	1974	1975	1976	1977	TOTAL
AFRICA					
Kenya	1,000	2,000	1,350	3,870	8,220
Subtotal	1,000	2,000	1,350	3,870	8,220
ASIA					
Korea, South	2,500				2,500
Malaysia	800				800
Sri Lanka*	550	600	600	24	1,774
Viet-Nam, Socialist Republic of	100	140	30	100	370
Subtotal	3,950	740	630	124	5,444
TOTAL	4,950	2,740	1,980	3,994	13,664

*50,000 cycles are scheduled for 1978 delivery.

Source: Ekroth, Swedish International Development Authority (50)

Table 6. Two Estimates of Number (in Thousands) and Percentage of Married Women of Reproductive Age (MWRA) Using All Methods of Contraception and Using Oral Contraceptives, by Source of Supply and Service in 36 Countries, Calculated by Population Council and US Agency for International Development, 1977

	Population Council Data						USAID Data	
	Commercial Sector		Government Sector		All Sources		Organized Programs	
	No. of Users	% of MWRA	No. of Users	% of MWRA	No. of Users	% of MWRA	No. of Users	% of MWRA
AFRICA								
Egypt[1] 1975								
All Methods					1,085	21	855.7	15.4
Orals					**555**	**11**	**587.7**	**10.6**
Ethiopia 1977								
All Methods							31.0	0.6
Orals							**30.3**	**0.5**
Ghana 1977								
All Methods			42.1	2.1	42.1	2.1		
Orals			**24.1**	**1.2**	**24.1**	**1.2**		
Kenya 1977								
All Methods							96.9	4.9
Orals							**52.9**	**2.7**
Mauritius 1978								
All Methods	4.2	3.4	61.6	49.2	65.8	52.5		
Orals	**3.7**	**3.0**	**32.9**	**26.3**	**36.6**	**29.2**		
Morocco[2] 1977								
All Methods							165.0	6.2
Orals							**125.0**	**4.7**
Tunisia 1977								
All Methods			137	17.0			199.3	21.9
Orals	**21.7**	**2.7**	**17.8**	**2.2**	**39.5**	**4.9**	**53.3**	**5.8**
Zaire 1977								
All Methods							12.2	0.3
Orals							**3.5**	**0.1**
ASIA								
Afghanistan 1977								
All Methods							23.7	1.1
Orals							**13.8**	**0.6**
Bangladesh 1977								
All Methods					1,600	8.9	1,716.6	12.8
Orals					**410**	**2.3**	**645.7**	**4.8**
Fiji 1978								
All Methods	3	3	31	34	34	38		
Orals	**2**	**2**	**5**	**6**	**7**	**8**		
Hong Kong 1977								
All Methods	164	32	234	45	316	64		
Orals	**56**	**11**	**87**	**17**	**143**	**28**		
India[3] 1977								
All Methods			24,949	23.9			26,082.0	24.4
Orals							**67.0**	**0.1**
Indonesia 1977								
All Methods			4,370	23.0			4,318.7	20.2
Orals			**2,563**	**13.5**			**2,524.9**	**11.8**
Iran[4] 1978								
All Methods	453	8.1	905	16.2	1,358	24.3		
Orals	**453**	**8.1**	**719**	**12.8**	**1,172**	**20.9**		
Korea 1977								
All Methods	1,035	21.7	1,059	22.2	2,094	43.9	1,440.2	28.2
Orals	**143**	**3.0**	**224**	**4.7**	**367**	**7.7**	**179.0**	**3.5**
Malaysia 1976								
All Methods	137	10	332	24	469	34		
Orals	**110**	**8**	**260**	**19**	**370**	**27**		
Nepal 1977								
All Methods							107.1	4.3
Orals							**29.3**	**1.2**
Pakistan[5] 1975								
All Methods					780	6	1,760.6	14.5
Orals							**695.3**	**5.7**

	Population Council Data						USAID Data	
	Commercial Sector		Government Sector		All Sources		Organized Programs	
	No. of Users	% of MWRA	No. of Users	% of MWRA	No. of Users	% of MWRA	No. of Users	% of MWRA
Philippines 1977								
All Methods			1,200	22.0	1,200	22.0	1,348.9	24.0
Orals			**560**	**10.5**	**560**	**10.5**	**468.4**	**8.3**
Singapore 1968								
All Methods	51	18	153	53	204	77.1	153.4	57.2
Orals	**9**	**3**	**40**	**14**	**49**	**17**	**40.0**	**14.9**
Taiwan 1977								
All Methods	583	27	830	38	1,413	65		
Orals	**56**	**3**	**110**	**5**	**166**	**8**		
Thailand[6] 1977								
All Methods			1,936	34.2			1,750.1	31.2
Orals			**918**	**17.3**			**642.9**	**11.5**
WESTERN HEMISPHERE								
Colombia[2] 1976								
All Methods	698.0	22.5	810	26.1	1,508	48.6	892.0	33.6
Orals	**108.8**	**3.5**	**394**	**12.7**	**502.8**	**16.2**	**409.5**	**15.4**
Costa Rica[2] 1976								
All Methods					78.8	33.7	112.0	48
Orals					**53.7**	**23.0**	**75.6**	**33**
Dominican Republic 1977								
All Methods	210	21	93	9.3	303	30.3	140.7	23.7
Orals			**60**	**6.0**			**86.5**	**14.7**
Ecuador 1975								
All Methods					51.7	6.3	96.2	12.0
Orals					**19.0**	**2.3**	**38.6**	**4.8**
El Salvador 1976								
All Methods	26	3.1	61	7.3	87	10.4	176.4	27.6
Orals	**8**	**0.9**	**32**	**3.8**	**40**	**4.7**	**52.1**	**8.2**
Guatemala 1977								
All Methods							66.9	7.6
Orals							**32.0**	**3.6**
Haiti 1976								
All Methods					41	5	192.0	19.9
Orals							**25.7**	**2.7**
Jamaica 1977								
All Methods							85.3	42.0
Orals							**46.3**	**22.8**
Mexico[7] 1976								
All Methods	800	9	1,015	12	1,815	21		
Orals	575	6	**225**	**3**	**800**	**9**		
Nicaragua 1977								
All Methods							62.2	22.5
Orals							**43.8**	**15.9**
Panama[8] 1975								
All Methods					175	44	59.8	31.9
Orals					**48**	**12**	**28.8**	**14.9**
Paraguay 1975								
All Methods							90.3	27.0
Orals							**55.1**	**16.4**
Peru[7] 1977								
All Methods							19.3	9.9
Orals							**9.6**	**4.9**
Total Orals Column	**1,546.2 (379.7)**[10]		**6,271.8 (1,463.0)**[11]		**5,362.7**[9]		**7,062.6**	
Estimated Total Program Use							**8,525.6**[12]	

Note: Population Council data are for January of specified year unless otherwise noted; 1978 data unpublished. AID data are for 4th quarter of 1977 unless otherwise noted.

[1]Egypt—USAID data based on 4th quarter 1976
[2]Morocco, Colombia, Costa Rica—USAID data for 2nd quarter 1977; PC, Costa Rica, women aged 20–49
[3]India—PC data as of March 1977
[4]Iran—PC estimate may not include discontinuations
[5]Pakistan—PC estimate based on World Fertility Survey: MWRA are aged 15–49
[6]Thailand—PC estimate based on World Fertility Survey
[7]Mexico, Peru—PC data as of June 1976
[8]Panama—USAID data for 3rd quarter 1977
[9]Thailand and Indonesia not included in column 5 (PC: All Sources)
[10]Excludes all countries included in column 7 (USAID: Organized Programs) and in IMS pharmacy audit (Table 1); includes Mauritius, Fiji, Hong Kong, Korea, Malaysia, Singapore, and Taiwan.
[11]Excludes countries for which USAID data are given in column 7 and 8 (USAID: Organized Programs)
[12]Total USAID OC users plus PC Government Sector OC users for those countries not included in column 7 (USAID: Organized Programs), i.e., 1,463.0.

Source: Nortman and Hofstatter (132); USAID, Office of Population (203)

Table 7. Percentage of Married Women of Reproductive Age Using Various Contraceptive Methods in Selected Developing Countries, as Reported in World Fertility Surveys, 1974–1976

Country	Date	Percentage of Married Women of Reproductive Age*								
		All Methods	OCs	Injectables	Sterilization	IUD	Condoms	Rhythm	Withdrawal	Other
ASIA										
Fiji	1974	40	8		16	5	6	2	2	1
Korea, South	1974	35	8	0.2	5	8	5	5	3	1
Malaysia	1974	33	— 16 —		4	1	3	2	2	6
Nepal	1976	2	0.4		1.6	0	0.2	0	0	0.1
Pakistan	1975	5	1		1	1	1	0	0	1
Sri Lanka	1975	33	2		10	5	2	8	2	4
Thailand	1975	33	14	2	8	6	0.4	———	3 ———	
LATIN AMERICA										
Colombia*	1976	42	13		4	8	2	6	5	4
Costa Rica	1976	64	22		13	5	9	5	5	5
Dominican Republic	1975	31	8		12	3	2	1	4	2
Panama*	1976	54	17		22	4	1	2	3	5

*Aged 15–44, except in Costa Rica and Panama, 20–49

Source: World Fertility Surveys (36, 43, 45, 57, 104, 112, 127, 140, 142, 190, 203)

from 9 to 59 percent of all contracepting couples. Over 95 percent of Chinese couples are estimated to be using some fertility control method (33, 88). Table 8 gives figures, from six different communes or work sites, gathered by F. Jaffe and D. Oakley during a fact-finding trip in 1977. While there is no evidence to justify extrapolating any of these figures nationwide, they do suggest considerable pill use in China.

Under the circumstances, estimates of oral contraceptive use worldwide are highly tentative and problematical. USAID officials have suggested a figure of about 55 million women (or couples) protected from unwanted pregnancy by orals (152, 185). The figure of 54 million as calculated in Table 9 includes an extremely rough estimate for the People's Republic of China—13 percent of the total population representing married women of reproductive age (a low percentage because of late ages of marriage) and 10 percent of those married women using OCs (a rate in the same range as that of Indonesia and the Philippines). Commercial sales covered by IMS do not include Scandinavia and Eastern Europe among the developed regions and much of Latin America, the Caribbean, and South Asia among the developing countries. Therefore, these figures all have wide margins of error. They are presented here to give a basis for estimating the worldwide prevalence of OC use in 1977.

Table 8. Percent Distribution of Birth Control Methods Used in Selected Places in China, 1977

Place	OCs	IUDs	Condoms	Sterilization	No method
Peking pharmaceutical factory	34	24	24	18	0
Wan-Tou commune	11	62	1	12	14
Chang-Ching commune	9	18	0	60	13
Shanghai municipality	25	15	13	46	1
Fushan silk factory	59	17	0	24	0
Fushan ceramic factory	26	13	0	51	10

Note: The percent distribution of methods was given as shown, but it was not clear whether the totals in the different places represented all married women of reproductive age or all contraceptive users.

Source: Jaffe and Oakley (88)

Table 9. Estimated Number of Oral Contraceptive Users Worldwide, 1977

	Millions of Women	
Developed Country Users		
Commercial Sales (IMS, Table 1)	21	± 2.0
Other Commercial Sales	3	± 0.5
Government Programs	4	± 0.5
Developing Country Users		
Commercial Sales (IMS, Table 1)	4	± 0.5
Other Commercial Sales (Table 6)	1	± 0.5
Government Programs (Table 6)	9	± 2.0
People's Republic of China		
900 million people × 13% estimated MWRA × 10% estimated usage	12	± 5.0
TOTAL	54	±11.0

EVALUATING SIDE EFFECTS

Research on the side effects of oral contraceptives, first reviewed in detail in **Population Reports** A-2 (March 1975), has continued and expanded. Hardly an obstetrics and gynecology journal appears without some mention of oral contraceptives in relation to symptoms, diseases, or laboratory measurements—reports which the popular media are quick to pass on to the public. In all languages all over the world readers are constantly warned about real or suspected hazards of steroidal contraceptives. Oral contraceptives are not only one of the world's most widely used drugs, they are also one of the most carefully scrutinized, by both medical and lay people.

Debates over methodology accompany each major study published on oral contraceptives, for, despite the volume of research, observation, and speculation, it remains difficult to reach conclusions about the relationships of OCs to various rare but serious illnesses. Therefore, most researchers are cautious about attributing previously unsuspected adverse or beneficial effects to the pill.

OCs have been known for some time to affect the risk of circulatory system diseases; particularly, they have been linked to clotting in the veins. The thrust of recent research is that OCs may affect a broader range of circulatory disorders than could be confirmed earlier, but that the increased risk may be largely confined to older women with conditions predisposing them to such diseases. These conditions include obesity, hypertension, high cholesterol levels, diabetes, and, most importantly, smoking.

The relatively low prevalence of smoking and other vascular disease risk factors in most developing areas, along with the low incidence of nonrheumatic circulatory system disease, suggests that, on the average, fewer circulatory system disorders will be associated with pill use in developing countries than in industrialized nations.

Outside the realm of circulatory system disease, recent studies reveal no substantial new risks associated with OC use. In fact, some concerns—particularly over effects on subsequent fertility and on offspring conceived after pill use—have been quieted by recent reports.

Recent Cohort Studies

Much of the knowledge of oral contraceptive effects gained in the last few years comes from ongoing cohort studies. Cohort studies—sometimes also called prospective studies—of oral contraceptives involve large numbers of women, some using OCs, some not, who are observed over a period of time to record the frequency of diseases in user and nonuser groups. The cohort study not only provides the opportunity to compare users and nonusers (often expressed as a ratio of event rates), but also indicates the absolute incidence of disease in each group. Cohort studies require extensive advance preparation, consistent record-keeping, long-term follow-up and, to study rare diseases, a very large number of participants. Thus they are difficult to organize and expensive to maintain. Ideally, participants should be designated users and nonusers on a random basis and not by individual choice. Since randomization is rarely possible with contraceptive use, the self-selection of OC users may introduce bias into cohort studies. Further, high dropout rates can raise questions about the validity of later findings. Yet cohort studies provide the most readily understood way to identify associations between contraceptive methods and health effects, especially those that had not been previously suspected, and to quantify those associations.

The three major cohort studies are the Royal College of General Practitioners' Oral Contraception Study in the United Kingdom, the Kaiser-Permanente Contraceptive Drug Study in Walnut Creek, California (USA), commonly known as the Walnut Creek study, and the Oxford/Family Planning Association (FPA) study in the UK. Early results from the first two studies were discussed at length in **Population Reports** A-2 (March 1975). In 1976, interim data from the Oxford/FPA study were published (213). The statistically significant results of the Oxford study are summarized in Figure 3. While all three are of cohort design, the studies differ in how they enrolled participants, what events they record, how they collect information, and how they report their data (see Table 10).

Case-Comparison Studies

An alternative study design is the case-comparison study (also called case-control). A group of women with a particular condition or illness (the cases) is selected, as is a comparison group of generally similar women who do not have the disease (controls). The current or previous use of oral contraceptives in the cases and controls is then compared. The controls are selected to be as similar to the cases as possible in ways likely to bear on OC use and the occurrence of the disease; if not, such potential confounding variables must be taken into account in the analysis of the data.

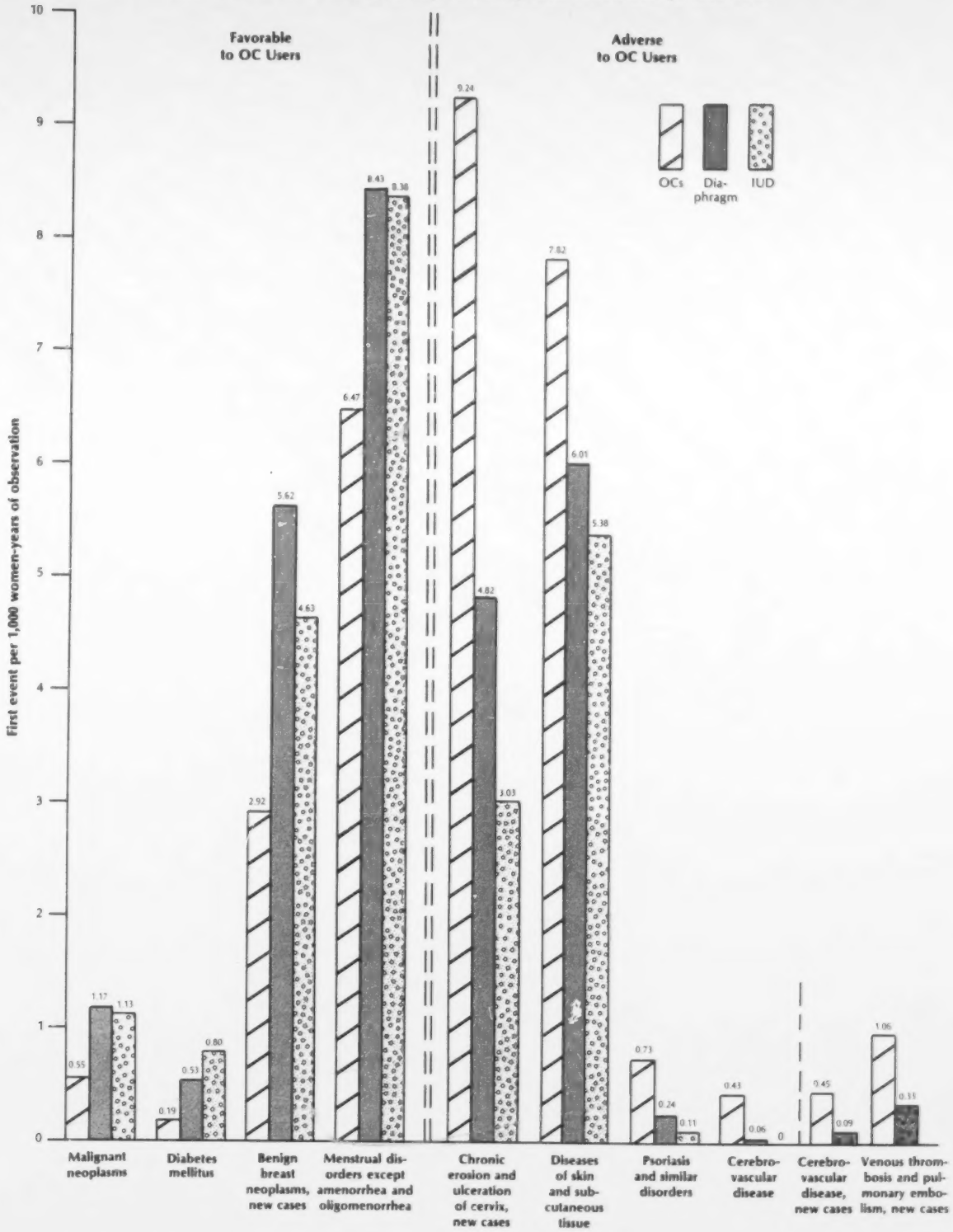
A case-comparison study is useful for studying rare illnesses because it does not have to wait for the cases to develop in the study population. The results of case-comparison studies are often summarized by "relative risk" estimates. These estimates actually compare OC use in cases and controls, not disease incidence; they are calculated by dividing the ratio of OC users to nonusers among the cases by the comparable ratio among the controls. Case-comparison studies cannot provide information on the overall incidence of a disease or detect previously unsuspected associations.

Vital Statistics Trends

Another method of investigating alleged relationships between OC use and disease is to look at vital statistics. Changes in the death rates from specific diseases over time can be compared with changes in OC use. Mortality rates changing in a pattern consistent with changes in OC use would raise the suspicion of an association between the two. If the trends for women of reproductive age diverged from those for men or older women in ways consistent with OC use trends, the suspicions would be strengthened. On the other hand, if mortality among women of reproductive age declined steadily or increasingly as oral contraceptive use increased—as appears to have often been the case recently—researchers would want to look more critically at the case-comparison and cohort studies and search for other evidence of cause-and-effect relationships as well as statistically significant relationships (155).

An analysis of trends cannot be expected to reveal small changes in disease incidence among OC users nor large changes either in small subgroups of the population or in groups in which OC use is rare. Furthermore, changes in other factors influencing incidence or mortality, variations or errors in diagnosis or codification of cause of death, and the difficulties of estimating OC use, especially in specific groups, make trend analysis difficult. Nevertheless, although it is not a substitute for cohort and case-comparison studies, it is a useful ancillary approach and check and would reveal whether any major increase in deaths due to OC use were occurring.

Figure 3. Rates of Various Conditions in Users of Oral Contraceptives, Diaphragms, and IUDs in the Oxford/Family Planning Association Study, 1968-1975



Conditions are shown for which the rate for users of oral contraceptives differed significantly ($p < 0.05$) from rates for diaphragm or IUD users. Contraceptive use status was determined by method in use at entry into study, except for cerebrovascular disease and venous thrombosis (at extreme right), which were calculated on the basis of the method actually used during follow-up, and which compare OC users with users of diaphragms and IUDs combined. Conditions for which significant differences appeared to be attributable largely to initial choice of method rather than to subsequent use are excluded. Based on 31,076 woman-years of observation of OC group, 14,739 of diaphragm group, 10,014 of IUD group. Rates standardized for age, parity, social class, and smoking.

Source: Vessey et al. (213)

Risk Estimates

Several points should be kept in mind when looking at epidemiologic studies and at the relative risk estimates or the mortality or incidence rates or ratios that are used to summarize their findings. First, epidemiologic studies do not prove causation. A determination of cause and effect is a conclusion based on consideration of many factors, including but not necessarily limited to epidemiologic evidence (78,111) (see **Population Reports** A-4, p. A71). An association might be noncausal, as, for example, when OC users have more bronchitis than nonusers—not because OCs cause bronchitis, but because OC users are more likely to smoke. Also, OC users in developed countries tend to have more contact with physicians than do other women, and physicians may treat suspected illnesses in OC users more carefully. A US study found, for example, that OC users were hospitalized 20 to 40 percent more often than nonusers, even for complaints unrelated to OC use (79). Similarly, the strength of any association between drugs and a health problem can be exaggerated by selecting controls less likely to bring their symptoms to the attention of a physician (80).

Second, the fewer the cases studied, the wider is the margin of error in estimated risk. For example, in the Royal College study it was calculated that mortality rates from circulatory system diseases were 4.9 times higher for OC users than for nonusers. With only 29 deaths to analyze there is a 95 percent chance (e.g., a 95 percent confidence interval) that the actual figure is somewhere between 1.7 and 14.0 instead of exactly 4.9. There is a 5 percent chance that this risk is less than 1.7 or more than 14.0 times the risk for nonusers (23,169).

Third, a rate ratio or relative risk estimate needs to be put in context. These summary measures compare two groups; they do not convey information about the incidence of disease in OC users or nonusers. For example, to put into context the recent finding of five times greater mortality in OC users than in never users (169), D. May pointed out that this rate ratio means that pill use decreased the chances of survival during a year from 99,995 per 100,000 to 99,974 per 100,000—a reduction of a negligible two-hundredths of a percent (121). Furthermore, as a recent WHO report pointed out:

> It is also important to bear in mind the frequency of the disease. For example, if the incidence of a disease is 1 per million among non-exposed persons, and the use of a particular drug increases the relative risk of disease tenfold, then one would anticipate 10 cases per million users of the drug. On the other hand, if the incidence of another disease is 100 per

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Table 10. Characteristics of Major Cohort Studies of Oral Contraceptives

Name, Year Initiated	Ref. No.	Source of Participants	Age Range	Number Enrolled	Information Recorded	Length of observation (as of most recent report)
Royal College of General Practitioners' Oral Contraception Study, 1968	167, 170	Patients of 1,400 volunteer general practitioners in the UK	15–49	Current OC users: 23,611 Never OC users: 22,766	Physicians' routine diagnoses	OC users (includes those beginning use during study): 60,632 woman-years Former users, abandoning OC use during study (not including resumption of use): 35,992 woman-years Never users (excluding experience after any started OCs during study): 110,065 woman-years
Oxford/Family Planning Association study, 1968	213, 215	Clients of 17 clinics in the Family Planning Association (UK)	25–49	17,032 total. OCs: 56% IUDs: 19% diaphragm: 25%	Answers to questions asked at return visits to clinics	By method at entry, regardless of subsequent methods: OCs: 49,681 woman-years IUDs: 16,209 woman-years Diaphragms: 22,937 woman-years
Kaiser-Permanente Contraceptive Drug Study, 1969	24, 25, 145	Women receiving general check-ups at Walnut Creek, California, clinic, 1969–1971	18–58	16,579 total	Answers to periodic mail & telephone questionnaires, diagnoses on return visits, clinic & hospital records	OC users: 65,000 woman-years of actual use Never users: 35,885 woman-years of observation
Boston area survey, 1970, 1973	79	Women residents of Boston (USA) area	26–50	1970: Ever OC users: 19,682 Never OC users: 46,161 1973: Ever users: 12,483 Never: 11,658	1970: 1969 hospitalizations 1973: 1970–1972 hospital-	1970: One year (1969) for each woman 1973: Three years (1970–72) for each woman

million, and drug exposure increases the risk only twofold, then one would anticipate 200 cases per million among users of the drug. This latter situation would clearly entail a greater public health problem, even though the relative risk is much smaller (201).

The seriousness of the disease must also be kept in mind. A slight decrease in a life-threatening condition like breast cancer, for instance, would outweigh a large increase in skin disease. Also, an awareness of the morbidity and mortality associated with other conditions, including pregnancy, can provide a perspective from which to judge the context of and alternatives to specific disease risk, as can comparisons with the risks and benefits of common activities that are not health-related, such as traveling, engaging in sports, or using tools and machinery.

Fourth, and most important to the interpretation of recent studies on OCs and vascular diseases, risk estimates are averages. They summarize and compare the experience of a whole group of study participants, for example, British women utilizing specific clinics or physicians. Like all averages, they tend to obscure the range they summarize. They do not apply to any specific subgroups that differ from each other in important ways. Further, if another factor acts synergistically with OC use—as appears to be the case with smoking in some circulatory system diseases—the statistical procedure of standardizing for that other factor will not remove its effect on a risk estimate. Stratification—examining separately those with the risk factor and those without—is necessary to accomplish that. Even then, when the increased risks are heavily concentrated in certain subgroups—such as women over 35 who smoke—it is difficult to determine accurately what the risks are for other subgroups, who may experience little change in risk. **The most important practical implication of recent studies on oral contraceptives and circulatory system diseases, reviewed below, is that different women face different risks in using OCs and that those facing special risks can now be more easily identified.**

CIRCULATORY SYSTEM DISEASE

The most disturbing findings of the two British cohort studies relate to circulatory system disease. Both the Royal College study and the Oxford/Family Planning Association study found that oral contraceptive users died from vascular disease at a higher rate than nonusers. Furthermore, a broader range of diseases was involved than had been previously found in case-comparison studies and earlier cohort data. The Royal College study also indicated that mortality rates increased with duration of oral contraceptive use and that even in women who discontinued orals the rate of mortality from circulatory disease was higher than in women who had never used them. Both analyses noted that a high proportion of the deaths in each study population was among women who smoked (see "Smoking, OCs and Circulatory System Disease," p. A-162 below).

As Table 11 shows, there were 101 deaths from all causes among the 46,000 women in the Royal College study—56 among women who had ever used the pill and 45 among the never users. The ever users had an overall death rate of 58.0 per 100,000 women-years compared with 40.9 for never users—a 40 percent difference. Twenty-four of the 56 deaths among pill users were attributed to circulatory disease in the categories of nonrheumatic heart disease, hypertension, and cerebrovascular disease, for a death rate of 25.8 per 100,000 woman-years, whereas only five of the never users died from circulatory disease, for a death rate of 5.5 per 100,000. The ratio of mortality rates for ever users as compared with the never users was therefore 4.7 to 1; in other words, 4.7 times higher in users. Comparing current users and never users the risk ratio was 4.9 to 1; comparing past users with never users, 4.3 to 1 (169).

Table 11. Rates of Mortality (per 100,000 Woman-years) from Various Causes, by Oral Contraceptive Use, in United Kingdom Cohort Studies, 1968–1977

	Royal College Study					Oxford/FPA Study				
	Ever users		Never users		Rate ratio (users/ never users)	OC users at entry		Diaphragm & IUD users		Rate ratio (OC users/ others)
Cause of death	Rate	No.	Rate	No.		Rate	No.	Rate	No.	
All neoplasia						21.6	10	28.3	12	0.8
All cancers	15.8	14	21.1	20	0.8					
All circulatory disease	25.8	24	5.5	5	4.7**	13.6*	7*	0	0	—
Nonrheumatic heart disease and hypertension	10.4	11	2.5	2	4.0*	9.8	5	0	0	—
Cerebrovascular disease	13.2	10	2.8	3	4.7*	3.8	2	0	0	—
Accidents and violence	17.1	16	10.0	9	1.7	3.4	2	6.8	2	0.5
Other causes	3.0	2	7.8	9	0.4	11.1	5	6.8	3	1.6
Total†	58.0	56	40.9	45	1.4	49.7	24	41.9	17	1.2

*$p<0.05$ **$p<0.01$

† Except for this category, all rates are standardized for age at entry into the study, parity, social class, and smoking. Standardization causes small discrepancies between individual and total rates.

Source: Royal College of General Practitioners' Oral Contraception Study (169); Vessey et al. (215)

While the ratio of mortality rates is similar to previous estimates of relative risks for specific circulatory system diseases (see **Population Reports** A-2), the difference in absolute mortality rates between users and nonusers is greater than would have been predicted on the basis of previous research (see Table 12*). The absolute risk was not the same for all women, however. Age, smoking, and duration of OC use all greatly affected the risk of death in the Royal College study, as shown in Table 13. For example, women over 45 died from circulatory system disease at the rate of 140 per 100,000 woman-years of OC use, as compared with 7.5 deaths per 100,000 for younger women, aged 15–24. For users who smoked the death rate was about 40 deaths per 100,000 compared with 14 per 100,000 among ever users who did not smoke.

Even these estimates do not entirely disaggregate the effects of various factors; for example, the difference in mortality rates for young nonsmokers using the pill for a short period would be less than any of the estimates shown in Table 13. Further disaggregation is difficult and, because of small numbers, would be hard to interpret. For example, the researchers note that "because of the small number of deaths in the nonsmokers only the excess deaths in smokers is statistically significant" (169).

With less than half as many woman-years of follow-up as the Royal College study, the Oxford/FPA study published in *Lancet* at the same time reported fewer deaths—43 compared with 101—but the distribution of mortality seemed to bear out some of the Royal College findings (215). All nine deaths due to circulatory disease occurred in women who were OC users when they entered the study. Seven were still users when they developed the illnesses that led to their deaths. Six smoked more than 10 cigarettes per day. The rate of mortality from all circulatory disorders in OC users was 13.6 per 100,000 woman-years of observation. (Two deaths were deleted from the analysis and from Table 11 because at the time of their deaths they were no longer participating in the study.) This figure is only half as large as the 25.8 per 100,000 mortality rate from circulatory disorders for ever users in the Royal College study. These differences arise from differences between the two populations studied and from the wide margin of error inherent in measurements based on a small number of deaths.

The Kaiser-Permanente Contraceptive Drug Study in Walnut Creek, California, will include data on circulatory system disease in its participants in a report expected in 1979.

In summary, in the larger British study, OC users' rates of death from circulatory system disease were high—about 40 per 100,000 women-years of observations—for both smokers and women over 35 and much lower—under 15 per 100,000—for nonsmokers and women under 35. In the smaller Oxford/FPA study, seven out of nine of the deaths were among women who smoked and seven of the nine women were 35 or older. There were no circulatory disease deaths among nonsmokers under age 35.

Table 13. Rates of Mortality (per 100,000 Woman-years) from Circulatory System Diseases, by Age at Death, Smoking Habit at Entry into Study, and Duration of OC Use, in the Royal College Cohort Study

	Ever Users	Controls	Absolute Difference
Age			
15–24	7.5	0	7.5
25–34	8.8	4.4	4.4
35–44	42.6	9.6	33.0
45–49	140.9	0	140.9
Smoking Habit			
Nonsmokers	13.8	3.0	10.8
Smokers	39.5	8.9	30.7
Duration of OC Use in Months*			
1–59	17.5	5.2	12.3
60+	50.5	5.2	45.3

*Age standardized

Source: Royal College of General Practitioners' Oral Contraception Study (169)

Subarachnoid Hemorrhage

The most striking finding of the Royal College mortality study (169) was the difference in deaths due to subarachnoid hemorrhage, a type of stroke thought to occur usually from rupture of congenitally weak walls of cerebral blood vessels. Five OC users (9.3 per 100,000 woman-years) and four former users (15.9 per 100,000 woman-years) died of subarachnoid hemorrhage, while none of the nonusers did. This accounted for roughly one-third of all nonrheumatic circulatory system disease deaths in users and one-half in former users (169). In the Oxford/FPA study, one death, in an OC user, was attributed to subarachnoid hemorrhage (215). The Royal College data suggest not only a link between OC use and subarachnoid hemorrhage, but also an effect that persists after a woman stops using OCs. Persistent effects had not been reported previously with any other circulatory system disease associated with oral contraceptives (see Table 14).

The Walnut Creek study in California has recently reinforced the Royal College data with evidence that the ratio of OC users to nonusers among 11 women hospitalized for subarachnoid hemorrhage was 6.5 times higher than the ratio among other study participants of the same age (144). Risk seemed to increase with duration of use. As in the Royal College study, a difference in risk persisted for former users in the Walnut Creek study—a relative risk of 5.4. In both studies, however, the numbers are small, and the evidence of a lingering risk does not yet seem conclusive. The Walnut Creek study revealed that smoking is also implicated in subarachnoid hemorrhage and, in fact, acts synergistically with OC use to increase dramatically the risk of the disease. The small number of cases among nonsmokers (three) made it impossible to determine relative risk for them separately. (See Table 15*.)

Subarachnoid hemorrhage accounts for about one-third of cerebrovascular disease deaths in US women of reproduc-

*Table 12, which summarizes selected studies of various circulatory system diseases and oral contraceptive use, appears on p. A-172.

*Table 15, which summarizes selected studies of venous thromboembolism, stroke, and oral contraceptive use, appears on p. A-174.

Table 14. Aspects of Various Circulatory System Diseases and Their Association with Use of Oral Contraceptives

Disease	Duration of use effect	Dose-response relationship	Persistence after OC use stops	Other known risk factors	Synergism of OCs with other risk factors
Myocardial infarction	Uncertain	Uncertain	No	Smoking Hypertension Hypercholesterolemia Diabetes	Yes Uncertain Uncertain Not studied
Venous thrombosis or pulmonary embolism	No	Estrogen Progestin ?	No	Smoking ? Diabetes Hypertension	Possibly not Possibly No
Cerebral thrombosis	Uncertain	Estrogen	No	Hypertension	No
Hemorrhagic stroke	Not studied	Not studied	Not studied	Hypertension Smoking	No Yes
Subarachnoid hemorrhage alone	Possibly	Not studied	Possibly	Smoking	Yes
Hypertension	Uncertain	Estrogen Progestin	No		

tive age. In this age group death rates are less than 10 per 100,000 and have declined since 1968 (see Figure 10). The fact that mortality rates for subarachnoid hemorrhage do not continue to rise with age for women past reproductive age, as they do for other circulatory system diseases, is a hint that natural hormones may play some role in the disease, but the problem of distinguishing subarachnoid hemorrhage from other strokes makes mortality data particulary susceptible to trends in diagnosis and, indeed, makes all epidemiologic studies of particular types of stroke difficult.

Heart Attack

In 1975 and 1976, a series of papers from Britain by J.I. Mann and colleagues provided the first strong evidence for a link between oral contraceptive use and heart attack. More recently US case-comparison studies have reinforced the British findings. Mann and colleagues studied separately both survivors of myocardial infarction and those who died from the illness (115, 116, 117, 118). In both studies, the relative risk of OC use for heart attack cases was approximately three (116, 117, 118) (see Table 16*).

The US studies show the same relationship, but varying degrees of risk. Two studies by L. Rosenberg and colleagues, after adjustment for other risk factors, estimated relative risks for OC use of less than two. The difference was statistically significant in the larger study (159 cases) (160), but not in the smaller (34 cases) (158, 159). A more recent report on 26 US cases and 59 controls found a much larger difference in OC use between the two groups: a relative risk of 14 (94). Although these women, unlike those in the other studies, did not have other conditions which might have increased their risk of heart attack (such as hypertension or diabetes), all but two were cigarette smokers. This would have independently increased their risk of heart disease. Only a very few young women who are nonsmokers have had heart attacks in any of these studies.

Mann and Inman could not associate risk of heart attack with estrogen dose in oral contraceptives (115), although an earlier study, based on a comparison of OC sales data and use patterns in women with circulatory system diseases, had suggested such a relationship (84). Indirect evidence from the Walnut Creek study suggests that heart attack risk may be related to the individual formulation of each oral contraceptive, with both the progestin and estrogen components playing roles. Looking at the level of high-density-lipoprotein (HDL) cholesterol in the blood sera of 4,978 women, 592 of them OC users, D.D. Bradley and colleagues found that the levels rose with estrogen dose and declined with progestin dose, although to varying degrees for different progestins, so that each contraceptive formulation had a unique effect (30). The net effect of some formulations was to raise HDL cholesterol levels; of others, to lower it; of still others, to cause no significant change from levels in nonusers.* Low levels of HDL cholesterol have been associated with high risk of coronary heart disease (66, 123, 156). The relationship of OCs and HDL cholesterol levels has appeared to be contradictory in other studies (10, 105), but when specific formulations are considered, the relationships seem to accord with the Walnut Creek findings (186).

Mann and colleagues' studies of fatal heart attacks illustrate the potential pitfalls of quantifying risk in epidemiologic studies. Initially half the available death certificates of women aged 40-44 were reviewed. Based on these 54 cases, researchers estimated a relative risk of approximately five; for women under age 40, the estimate was approximately three (115). On the basis of these findings, the US Food and Drug Administration (USFDA) added to the mandatory

*Table 16, which summarizes selected studies of myocardial infarction and oral contraceptive use, appears on p. A-177.

*Of the two oral contraceptives distributed by USAID, Norinyl 1+80 (®Syntex (F.P.) Inc., Humacao, Puerto Rico) increased HDL cholesterol levels significantly ($p < 0.05$), and Norinyl 1+50 (®Syntex) increased levels very slightly and not significantly.

language that appears on OC package labelling in the USA a recommendation that women over age 40 "be urged to utilize other forms of contraception" (206). Subsequently, Mann and colleagues examined the rest of the available data on cases aged 40-44. Adding another 54 cases to their analysis lowered the relative risk estimate to 2.8—virtually identical to the estimate for younger women (117). The apparent effect of age on relative risk had disappeared. If, by chance, Mann and colleagues had analyzed the latter cases first, they would have found no association between heart attack and pill use. The USFDA's warning to older women is not unfounded because absolute rates of myocardial infarction rise with age in both users and nonusers. Nonetheless, the basis for the recommendation is not as strong as it first appeared.

Mann and colleagues estimated on the basis of their studies that in England and Wales the mortality from heart attack attributable to OCs would be about 3.5 per 100,000 annually in women aged 30–39 (115). However, given the fact that, among heart attack survivors studied, nearly all cases either smoked or had other predisposing factors (118), this estimate would appear to be applicable only to women with one or more risk factors—perhaps 30 percent of women aged 30–44, judging by the control group (135). If so, attributable mortality in England and Wales might average about 2.5 per 100,000 annually in the 30–39 age group. It would be higher in older women and lower—perhaps much lower—among younger women. In the US, where fewer women smoke, and the types of pills used are more often those which depress HDL cholesterol levels less or elevate them more than do those used in Britain (186), heart attack mortality attributable to OCs would be even less. For the individual, it is clear that her risk depends greatly on whether she has any of the traditionally recognized risk factors for heart attack. Estimates of attributable mortality derived from work by A.K. Jain are 7.6 deaths per 100,000 OC users annually among smokers but only 0.4 among nonsmokers (89).

Venous Thromboembolic Disease

Venous thromboembolic diseases were the first circulatory system illnesses suspected of an association with oral contraceptive use (97). Today this association seems firmly established; the findings of British and US case-comparison studies of the late 1960s and early 1970s have been confirmed by the three major ongoing cohort studies (see Table 15). The Royal College study, after almost 34,500 woman-years of observation of OC users and over 47,000 of nonusers, reported first occurrences of deep leg vein thrombosis more than four times more often in users than in nonusers, even when no one in either group had predisposing conditions. Less than one case (0.82) developed per 1,000 woman-years of OC use. Far less serious superficial thrombosis of the leg occurred about 2.5 times more frequently in users than in nonusers, and at a rate of about 1.9 per 1,000 woman-years in OC users. There is no evidence that the effect persists after OC use stops (170).

Similarly, the Oxford/FPA study found that slightly more than one first diagnosis of venous thromboembolism occurred per 1,000 woman-years of OC use. The rate for IUD or diaphragm users was about one per 3,000 (213). A case-comparison analysis of data from Walnut Creek also found a significant link between venous thromboembolic disease and OCs when the condition occurred in women without predisposing factors. The ratio of OC users to nonusers was 7.7 times higher in the cases than in the controls (146).

The risk of venous thromboembolic disease has long been thought to be tied to the estrogen dose in oral contraceptives (84). This observation was reaffirmed by a 1975 US case-comparison study (192) and the interim report from the Royal College (167). A more recent Royal College report, however, found the estrogen dose effect limited to superficial vein thrombosis of the leg and not applicable to deep vein thrombosis (170). Such an analysis is difficult, the researchers point out, because there are two different estrogens in oral contraceptives, which may have differing effects and which interact with various progestins in different ways (46). Furthermore, the effect of OCs may be influenced by the progestin component as well. Among women using oral contraceptives containing the same dose of the same estrogen but three different doses of the same progestin, rates of superficial vein thrombosis, but not deep vein thrombosis, rose with the progestin dose (see Table 15). This relationship with progestin dose had not been reported previously (170).

The basic positive association between OCs and venous thromboembolism is supported by laboratory as well as epidemiologic evidence. Using plasma fibrinogen chromatography to detect "silent" thrombi—that is, thrombi without clinical manifestations—US researchers examined blood samples from 154 women before and during oral contraceptive use. Silent thrombi were discovered four to five times more often during OC use than before. The researchers point out that this parallels the ratio of diagnosed venous thromboembolic disease reported from epidemiologic studies of OC users and nonusers (4). British researchers, using the uptake of radioactive fibrinogen at sites of deep vein thrombosis to detect the disease, found post-operative deep vein thrombosis in 6 of 31 users but in none of 19 similar nonusers (175).

Since the association of venous thromboembolism and OC use has been widely known for a decade, users of oral contraceptives may be more likely than nonusers to see a doctor for leg pain and to have their symptoms attributed to thromboembolic disease. Recently, researchers in the US, using an objective diagnostic method to look for thrombi in women referred to them with clinical diagnoses of venous thrombosis, found thrombi in only 16.7 percent of 54 OC users but in 30.7 percent of 75 nonusers. The implication is that physicians attribute symptoms to thromboembolism more readily in OC users than in nonusers (15). If this type of bias operated in an epidemiologic study, it would tend to inflate the estimate of risk associated with OC use.

Explorations into the mechanism of thrombus formation in OC users continue to associate changes in various characteristics of the blood with OC use (14, 31, 72), but how those changes might lead to thrombus formation is still not known.

The overall excess mortality from venous thromboembolism that has been attributed to the pill is about 2 to 3 per 100,000 women annually. Studies have not shown that duration of use increases this risk.

Hypertension

No startling new information regarding the relationship of oral contraceptives and hypertension has emerged in the last few years. Studies have confirmed what was thought earlier: while using oral contraceptives most women have slightly higher blood pressures than do nonusers, but blood pressure drops after use is discontinued. In a few this rise will result in a diagnosis of hypertension, the number depending upon the criteria chosen to define the disease (see Table 17*). The issues remaining unresolved involve the roles of the two pill components, the estrogen and the progestin, and whether blood pressure continues to rise as the duration of use lengthens.

The Walnut Creek researchers looked extensively at blood pressure and diagnoses of hypertension in 13,358 women (58). A comparison of users with women who had never used OCs showed systolic readings averaging about 4.5 mm Hg higher in the users and diastolic readings about 1.5 mm Hg higher. About four percent of users, compared with 1.5 percent of never users, were diagnosed as having high blood pressure (>140/90 mm Hg). After discontinuation, mean blood pressures and the percentage diagnosed as having high blood pressure both were lower in former users than in never users.

The study also looked at women who changed contraceptive method. Women who began using OCs experienced a rise of about 4 mm Hg in systolic pressure and about 1 mm Hg in diastolic pressure. Women who abandoned oral contraceptives experienced decreases slightly larger than the increases. The data suggest that these changes are roughly the same in all women, rather than the result of a few extreme cases influencing the averages (58). In fact, women who developed hypertension or preeclampsia during pregnancy, and so might seem particularly susceptible to hormone-induced blood pressure changes, have not proved particularly likely to develop hypertension while using OCs (147).

The Walnut Creek study found no increase in blood pressure with lengthening duration of OC use. Other studies have, however. In the Royal College study, diagnoses of high blood pressure during the first year of OC use differed little between user and never-user groups, but rose steadily with longer use of OCs to 2 to 2.5 times higher in the fifth year of use than in the first (167). The Boston area mail survey of the early 1970s also detected an apparent increase in the hospitalization rate for hypertension that was correlated with length of OC use. Perhaps 20–40 percent of the difference may have been due to OC users generally being hospitalized more frequently than nonusers (79).

In contrast to most other major studies, the Oxford/FPA cohort study detected no significant difference in hypertension rates among its three groups of participants—OC users, diaphragm users, and IUD users (213). First diagnosis of hypertension occurred at a rate of about 1.6 per 1,000 woman-years among OC users, about 1.7 among diaphragm users, and about 0.7 among IUD users.

*Table 17, which summarizes selected studies of hypertension and oral contraceptive use, appears on p. A-179.

Figure 4. Packaging of oral contraceptives and other pharmaceuticals, originally performed only in developed countries, is gradually being shifted to the developing countries.

While OC-related blood pressure changes are slight and apparently reversible, any rise in blood pressure means some increase in the risk of stroke and coronary artery disease; there is no threshold beyond which high blood pressure suddenly becomes dangerous. In some cases, women already at high risk of developing stroke or heart disease—because of smoking, obesity, low glucose tolerance, a history of arterial disease, or high lipid levels in the blood—might wish to avoid the slight increase in blood pressure associated with OCs.

Initially, research suggested that the estrogen component of the pill was responsible for the rise in blood pressure (44, 187). But a recent report from the Royal College study implicated the protestin component as well. Among study participants were women using three different oral contraceptives, all with the same amount of the same estrogen but with varying amounts of the same progestin. The rates of first diagnoses of hypertension in the groups rose with the amount of progestin in their pills (168) (see Table 17).

In summary, blood pressure appears to rise during OC use but to decline after discontinuation, sometimes to levels slightly below those before OC use began. In the Walnut Creek study 4 percent of users, compared with 1.5 percent of nonusers, were diagnosed as having high blood pressure (58). Reports on whether blood pressure rises with duration of use are in conflict. To what extent higher blood pressure during OC use contributes to excess mortality in OC users and whether lower blood pressure after discontinuation remains lower and so contributes to reduced mortality later are still unresolved questions.

VITAL STATISTICS TRENDS

Mortality rates provide an additional source of evidence on OC use and circulatory system disease, but their analysis has been relatively neglected. Of the few studies published, most have dealt with venous thromboembolic diseases in the United States or in England and Wales. These studies found trends during the 1960s consistent with the contention that OC use increased mortality from these diseases. Studies of mortality rate trends for other circulatory system diseases produced mixed findings (see Table 18*).

The increased risk of death from circulatory system disease which the British and US cohort studies now associate with oral contraceptive use has posed with new urgency the question: are these estimated increases, which would multiply the risk of death from circulatory disease among OC users by a factor of five, reflected in higher death rates in countries where a high proportion of women have used orals?

To answer this question, R.T. Ravenholt and W. Rinehart have prepared charts of age-specific mortality rates for several circulatory system diseases (154, 155). Some of these charts are presented as Figures 5–12. An inspection of these charts on female mortality from circulatory system diseases in the United States, England and Wales, and Denmark during the last two decades does not suggest major changes in death rates attributable to OC use (see Figures 5, 7, and 8). In the United States, mortality rates for all circulatory system diseases decreased in the 1950s more rapidly in younger women than in older groups. Then in the 1960s the rapid declines moderated for women aged 25–44. In the 1970s, rates of mortality from all circulatory diseases have shown rapid and parallel declines for all age groups despite the fact that OC sales increased by roughly one-third during the early 1970s. Sharply declining death rates for hypertension contributed substantially to the decline (see Figure 6). In England and Wales, all age groups except the oldest (75 years and older) show death rates declining at similar paces. In Denmark, trends for the three 10-year reproductive age groups diverge. In none does the trend seem compatible with a major impact of OC use, which began in 1966. The failure of mortality to fall among Danish women aged 35–44 would be consistent with an effect of OC use among this more susceptible age group. Rates of use in this age range may be low, however, and the trend parallels those for older age groups. Therefore the meaning of the trend is unclear.

What appears to be a discrepancy between vital statistics trends and the risk estimates of recent cohort and case-comparison studies is beginning to draw the attention of researchers. As H. Ory of the US Center for Disease Control recently pointed out:

> Applying the age-specific death rates from the Beral report [Royal College of General Practitioners' Oral Contraception Study (169)] to the United States women, I estimate that nearly three-quarters of the cardiovascular disease deaths occurring annually in the United States to women of reproductive age would be attributable to OC use. This does not seem possible. US vital data showed that cardiovascular disease death rates have been falling nearly equally and steadily for men and women of reproductive ages since 1950. If OCs were as powerful a cause of cardiovascular disease as Beral's results suggest, I would expect death rates from these diseases to diverge for men and women (136).

To put the point in an even more elementary fashion, in 1960 the US death rate for circulatory system diseases was approximately 20 per 100,000 women aged 25–34. By 1975, the apparent peak year of oral contraceptive usage in the US, about one-fifth of all women aged 25–34 were using OCs. The Royal College study calculates a risk ratio of two, that is, a doubling of death rates from circulatory disease among OC users in this age group. Applying that ratio to the 1960 US death rates would, other things being equal, lead one to predict a 1975 US circulatory disease death rate of 24 per 100,000 aged 25–34.

Nonusers		**Users**		
$(20/100{,}000)(4/5)$	+	$(2 \times 20/100{,}000)(1/5)$	=	24/100,000

Actually, in 1975, the circulatory disease death rate for US women aged 25–34 was only about 12 per 100,000, 40 percent lower than in 1960 before OCs were used, rather than 20 percent higher, as predicted. Obviously other factors are also influencing these death rates, including changes in diet, exercise, and medical care, but if the risks of OC use in the US were of the magnitude that the Royal College study suggests, it would be necessary to hypothesize that these countervailing changes were even greater in magnitude in order to cancel out any increases in mortality caused by OC use.

Cerebrovascular Disease

In the Royal College study (169) nine of the deaths from circulatory system disease among OC users (and none among never users) were attributed to subarachnoid hemorrhage. Thus vital statistics trends for cerebrovascular diseases deserve particular attention. Mortality rates for cerebrovascular diseases as a group remained fairly constant among US women under age 40 throughout the 1950s and most of the 1960s. Recently, however, they have declined at a pace similar to those for older women, joining the trend these rates have exhibited over the last 25 years (see Figure 9). In England and Wales mortality from cerebrovascular disease among young women has changed little since OCs became available in 1961 (see Figure 11).

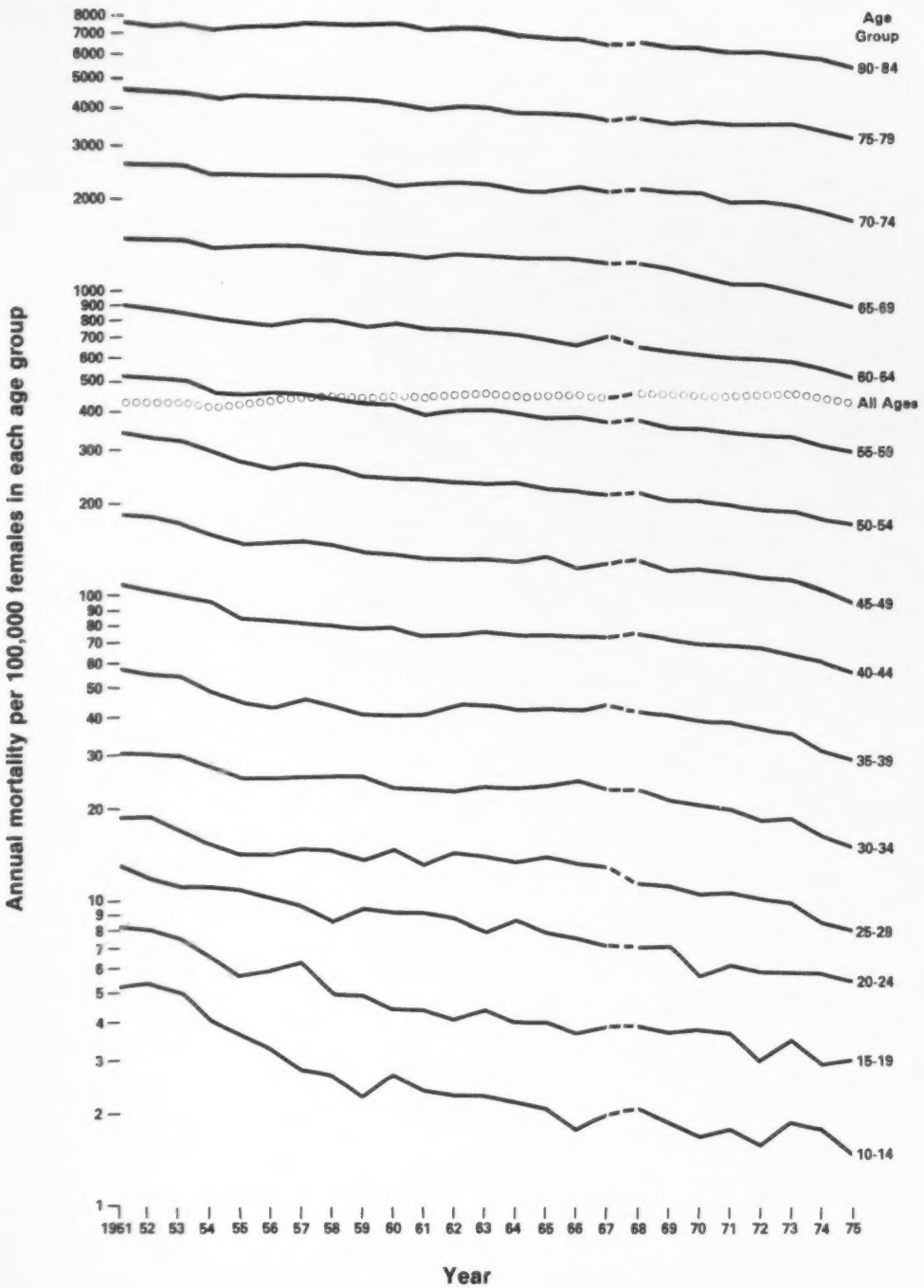
In Denmark the trend has been toward increasing mortality rates for cerebrovascular disease for females aged 35-54 during the 1970s, while the rates for the over-55 age groups steadily declined (see Figure 12). These trends would be consistent with an OC effect but are inconsistent with those in the United States and England and Wales.

US mortality rates for subarachnoid hemorrhage increased for all age groups over age 20 during the 1950s and 1960s but have decreased for all age groups during the 1970s (see Figure 10). The beginning of the decline seems to precede the recent drop in OC use in the USA.

L.P. Chow, looking at the prevalence of pill use and rates of mortality from stroke in Taiwanese women, found no significant correlations in any of the five-year age groups between 20 and 49. He concluded that the pill has not had an apparent adverse effect on female mortality from stroke in Taiwan. Less than five percent of married women in any five-year age group, however, used orals during this period. Mortality rates for women declined slightly since

*Table 18, which summarizes selected studies of trends in vital statistics and oral contraceptive use, appears on p. A-181.

Figure 5. Mortality from All Circulatory System Diseases,* Females, Aged 10–84, by 5-Year Age Groups, USA, 1951–1975

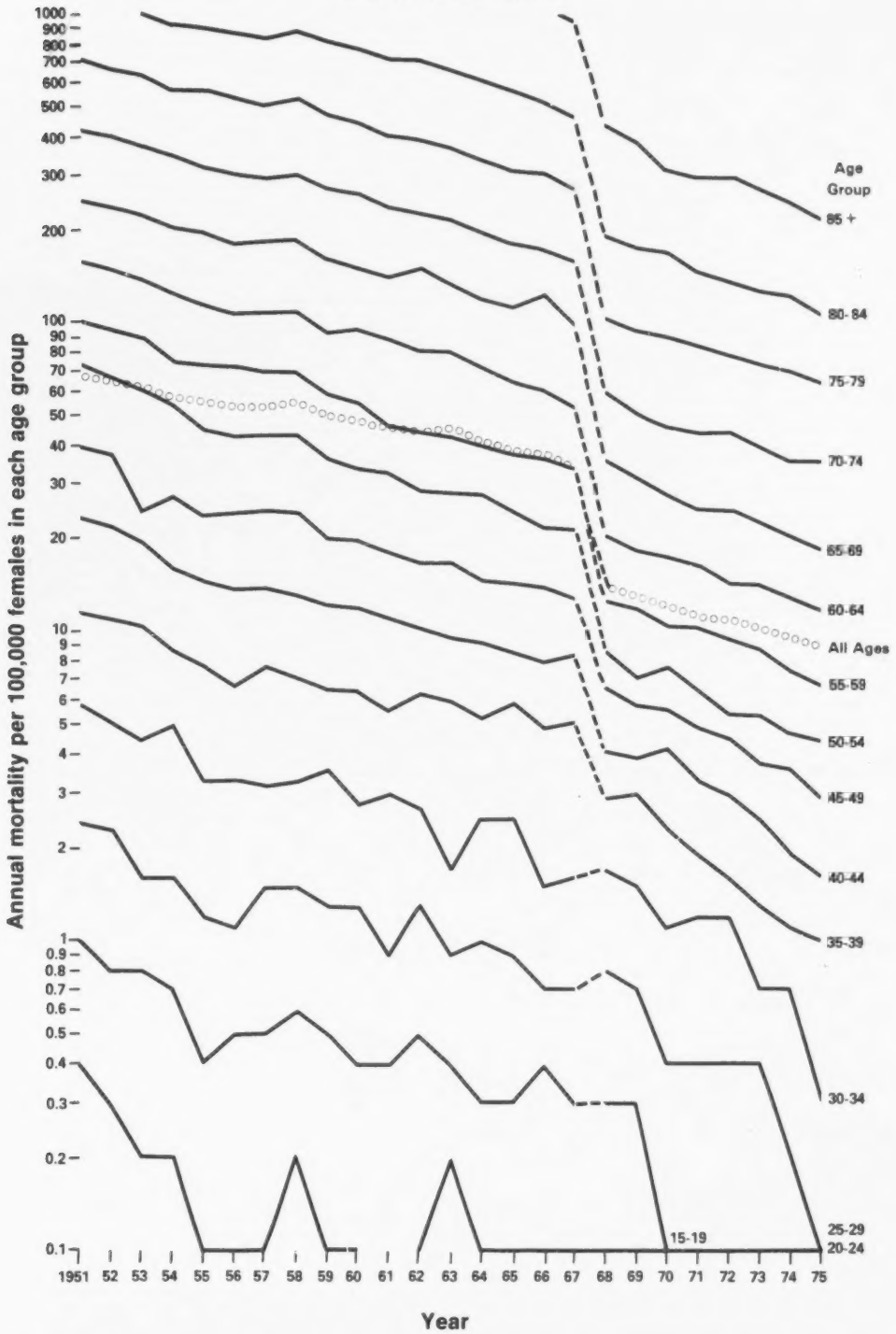


Mortality rates for all circulatory system diseases declined rapidly for US females of all ages during the 1950s, leveled off somewhat for females of reproductive age during most of the 1960s, and decreased rapidly for females of all ages during 1968–1975.

*ICD 390–458 (1968–1975); ICD 330–334, 400–468 (1951–1967)

Source: Ravenholt and Rinehart (155) based on data from US National Center for Health Statistics (207)

Figure 6. Mortality from Hypertensive Disease,* Females, Aged 15 and Older, by 5-Year Age Groups, USA, 1951-1975

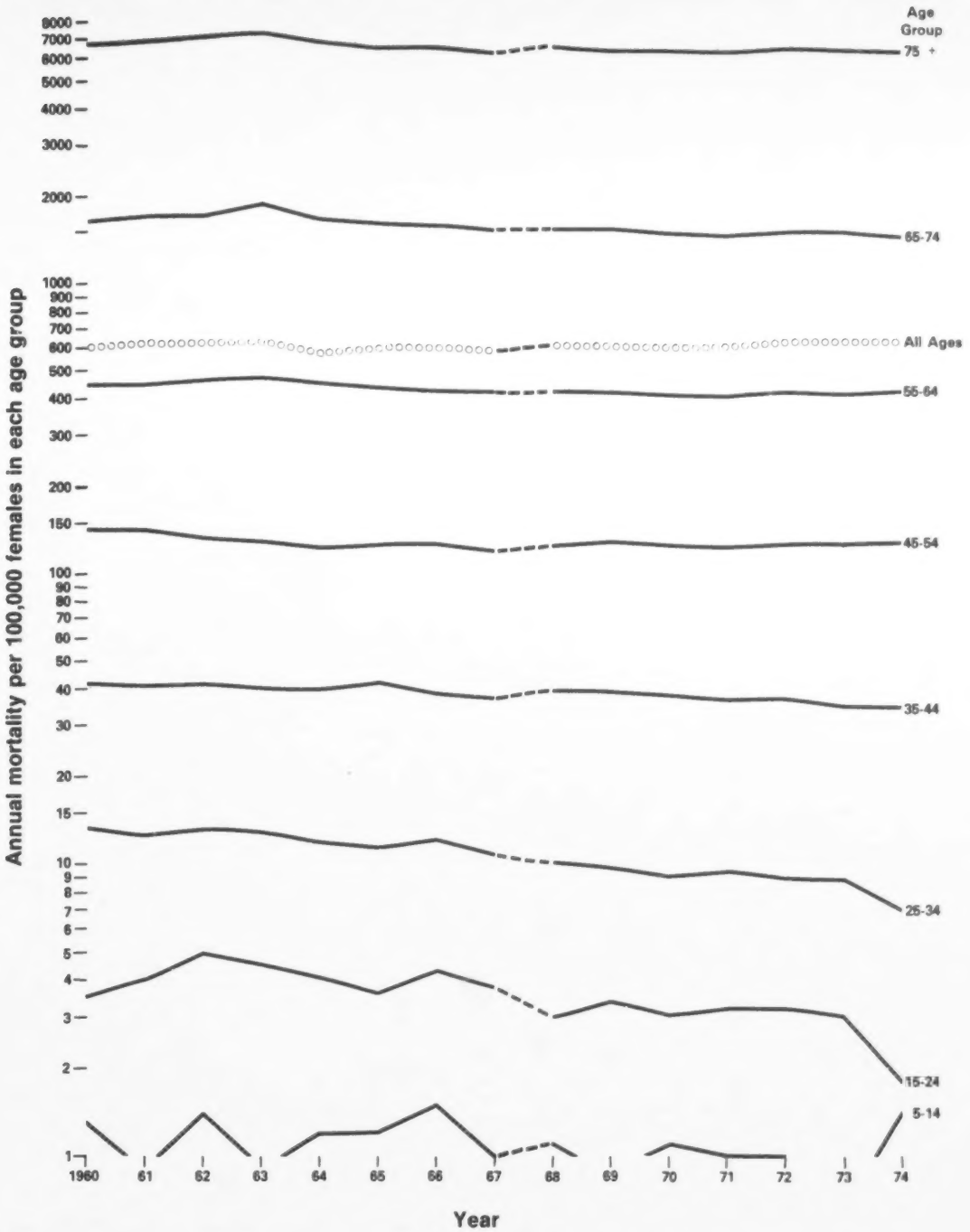


Mortality rates for hypertensive disease decreased dramatically for females of all ages during the last 25 years—especially during the 1970s for those of reproductive age.

*ICD 400–404 (1968–1975); ICD 440–448 (1951–1967)

Source: Ravenholt and Rinehart (155) based on data from US National Center for Health Statistics (207)

Figure 7. Mortality from All Circulatory System Diseases,* Females, Aged 15 and Older, by 10-Year Age Groups, England and Wales, 1960–1974

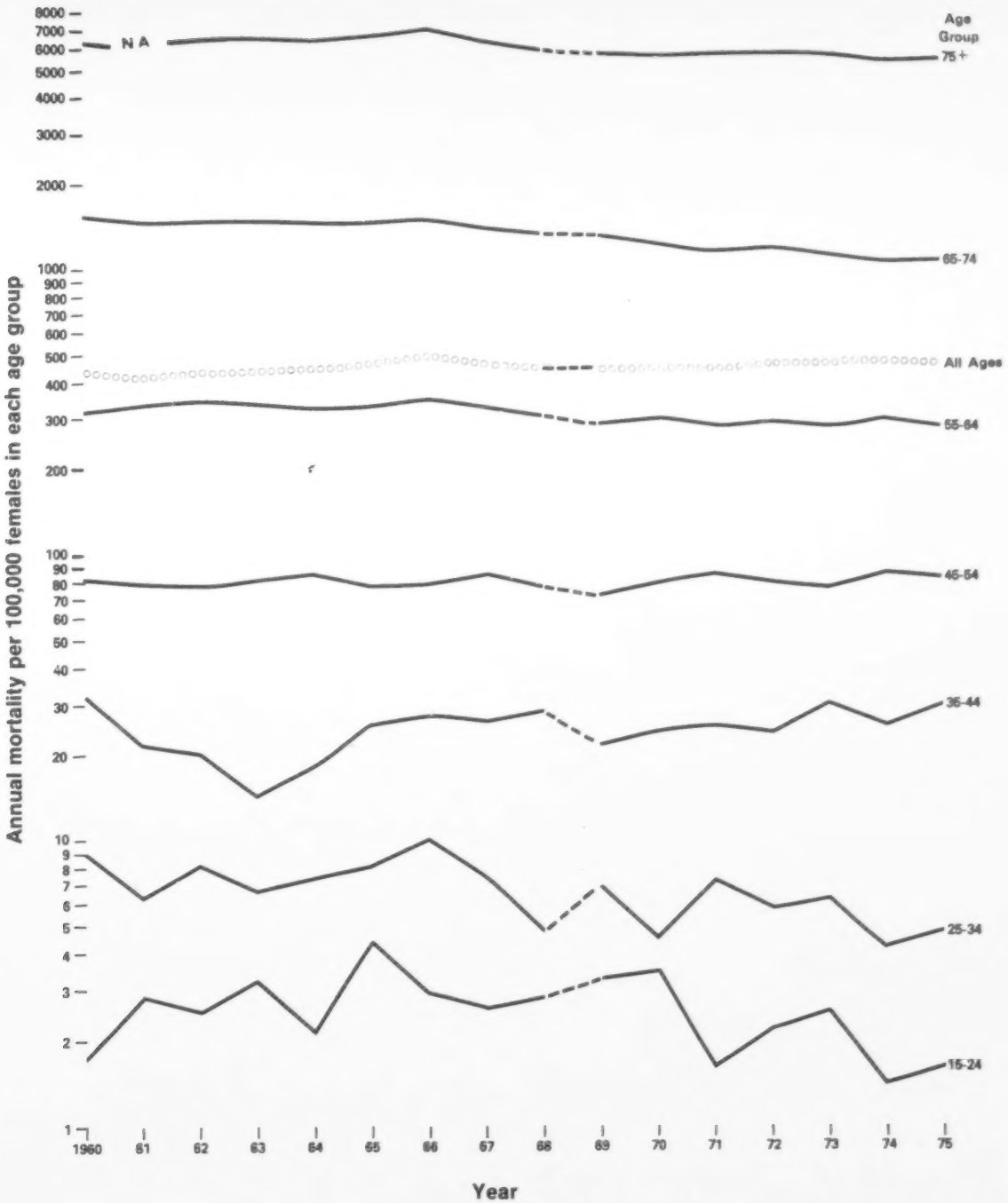


Mortality rates for all circulatory system diseases remained steady for females over age 44 in England and Wales but declined for females of reproductive age.

*ICD 390–458 (1968–1974); ICD 330–334, 400–468 (1960–1967)

Source: Ravenholt and Rinehart (155) based on data from WHO (202)

Figure 8. Mortality from All Circulatory System Diseases,* Females, Aged 15 and Older, by 10-Year Age Groups, Denmark, 1960-1975

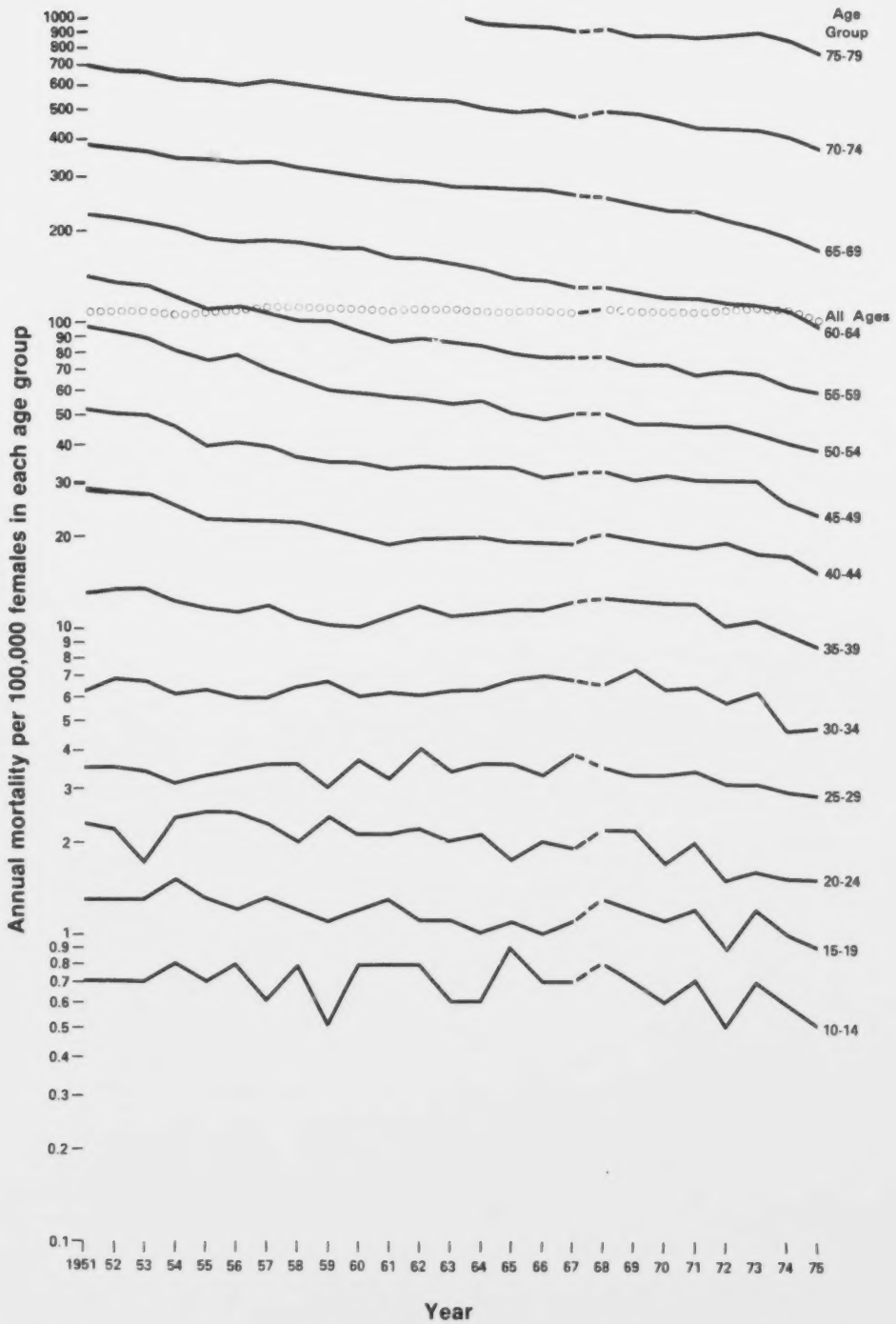


Mortality rates for all circulatory system diseases changed little in Denmark from 1960 to 1975, except that during the last decade rates decreased for females aged 15-34.

*ICD 390-458 (1969-1975); ICD 330-334, 400-468 (1960-1968)

Source: Ravenholt and Rinehart (155) based on data from WHO (202)

Figure 9. Mortality from Cerebrovascular Disease,* Females, Aged 10–79, by 5-Year Age Groups, USA, 1951–1975

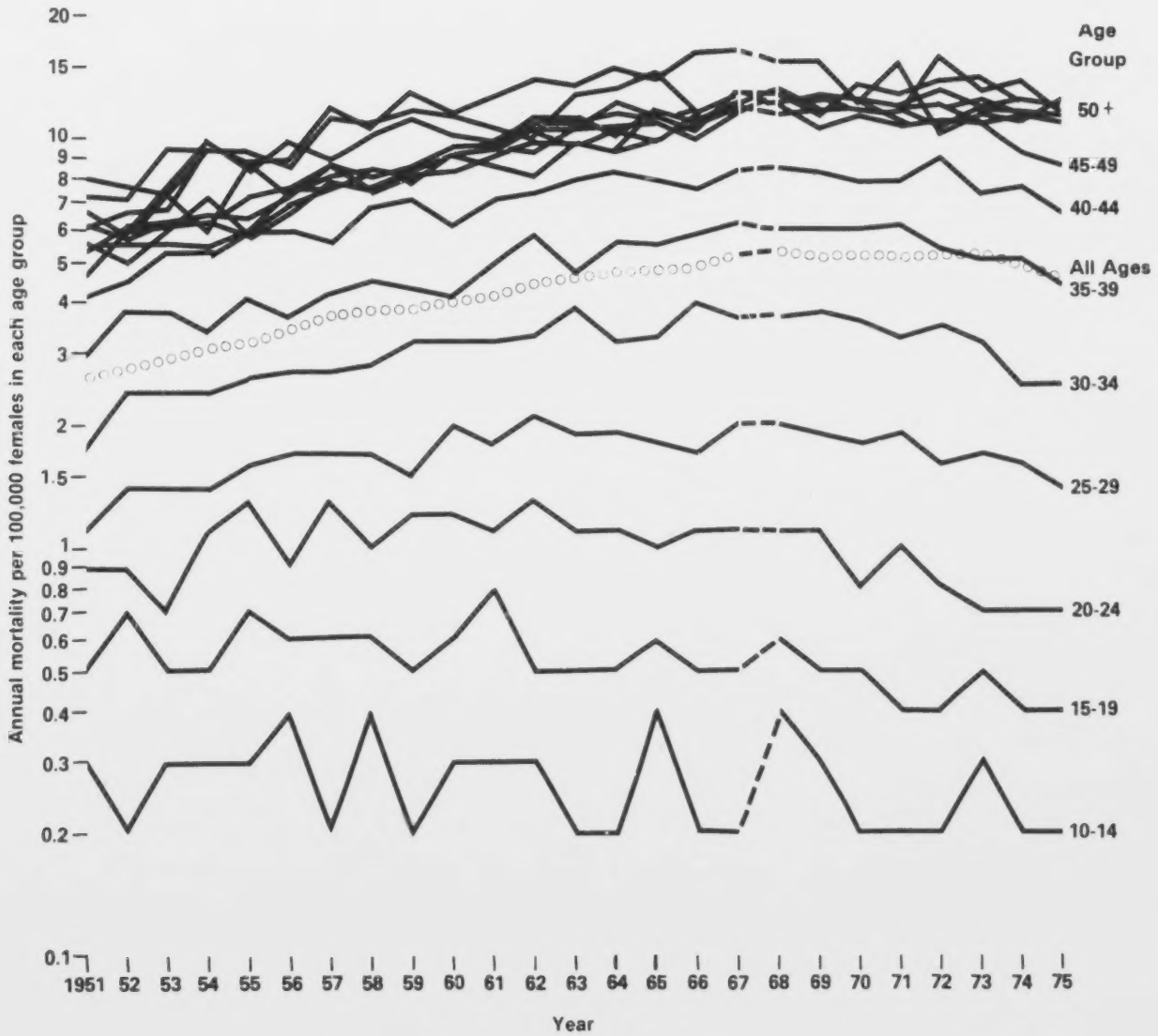


Mortality rates for cerebrovascular disease decreased steadily for females over age 49 from 1951 to 1975, whereas for females of reproductive age the trends leveled off during the 1960s, then resumed the decrease during the 1970s.

*ICD 430–438 (1968–1975); ICD 330–334 (1951–1967)

Source: Ravenholt and Rinehart (155) based on data from US National Center for Health Statistics (207)

Figure 10. Mortality from Subarachnoid Hemorrhage,* Females, Aged 10 and Older, by 5-Year Age Groups, USA, 1951-1975

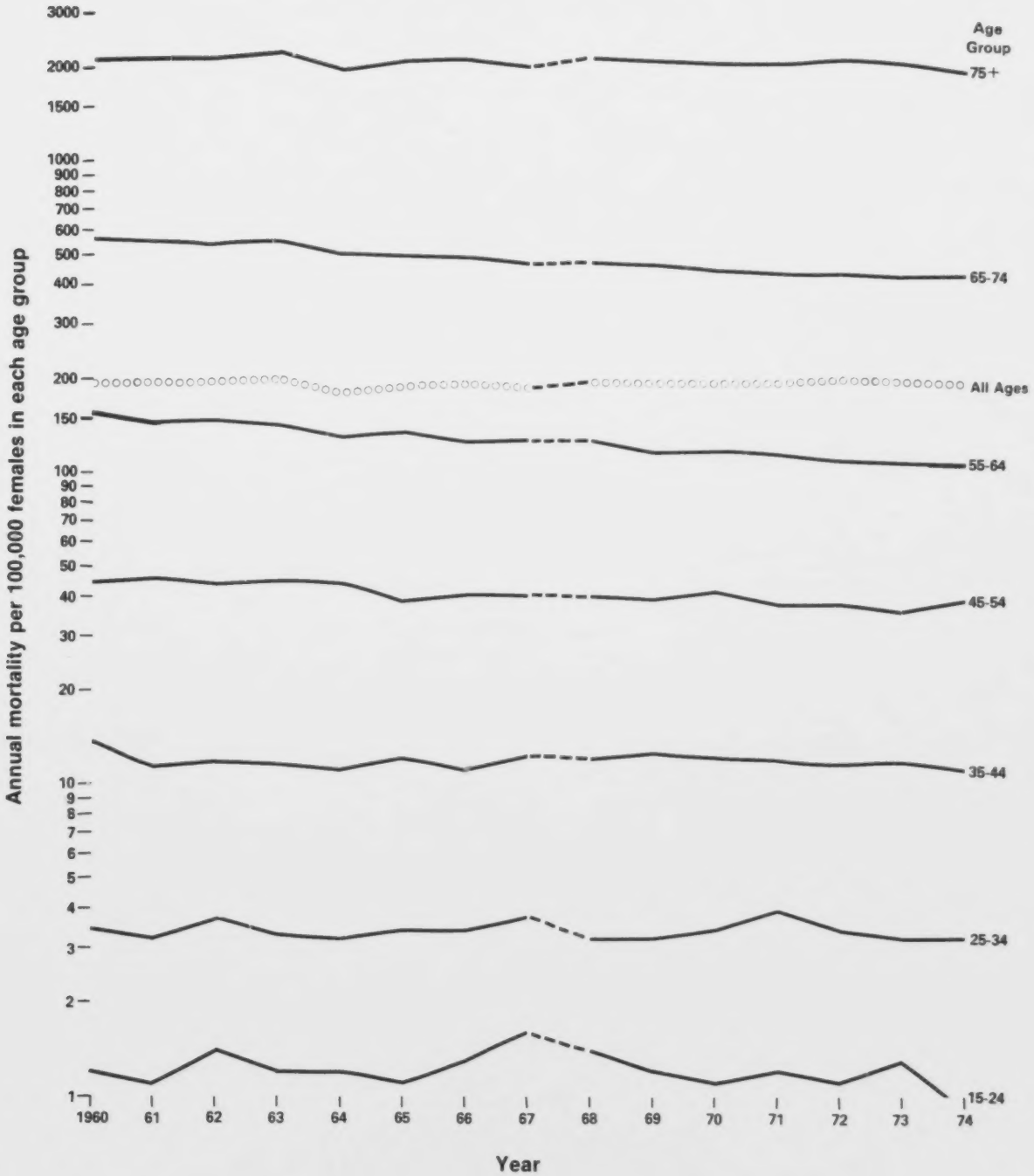


Mortality rates for subarachnoid hemorrhage increased for females over age 24 during the 1960s but have decreased since 1969 for those under age 50.

*ICD 430 (1968-1975); ICD 330 (1951-1967)

Source: Ravenholt and Rinehart (155) based on data from US National Center for Health Statistics (207)

Figure 11. Mortality from Cerebrovascular Disease,* Females, Aged 15 and Older, by 10-Year Age Groups, England and Wales, 1960-1974

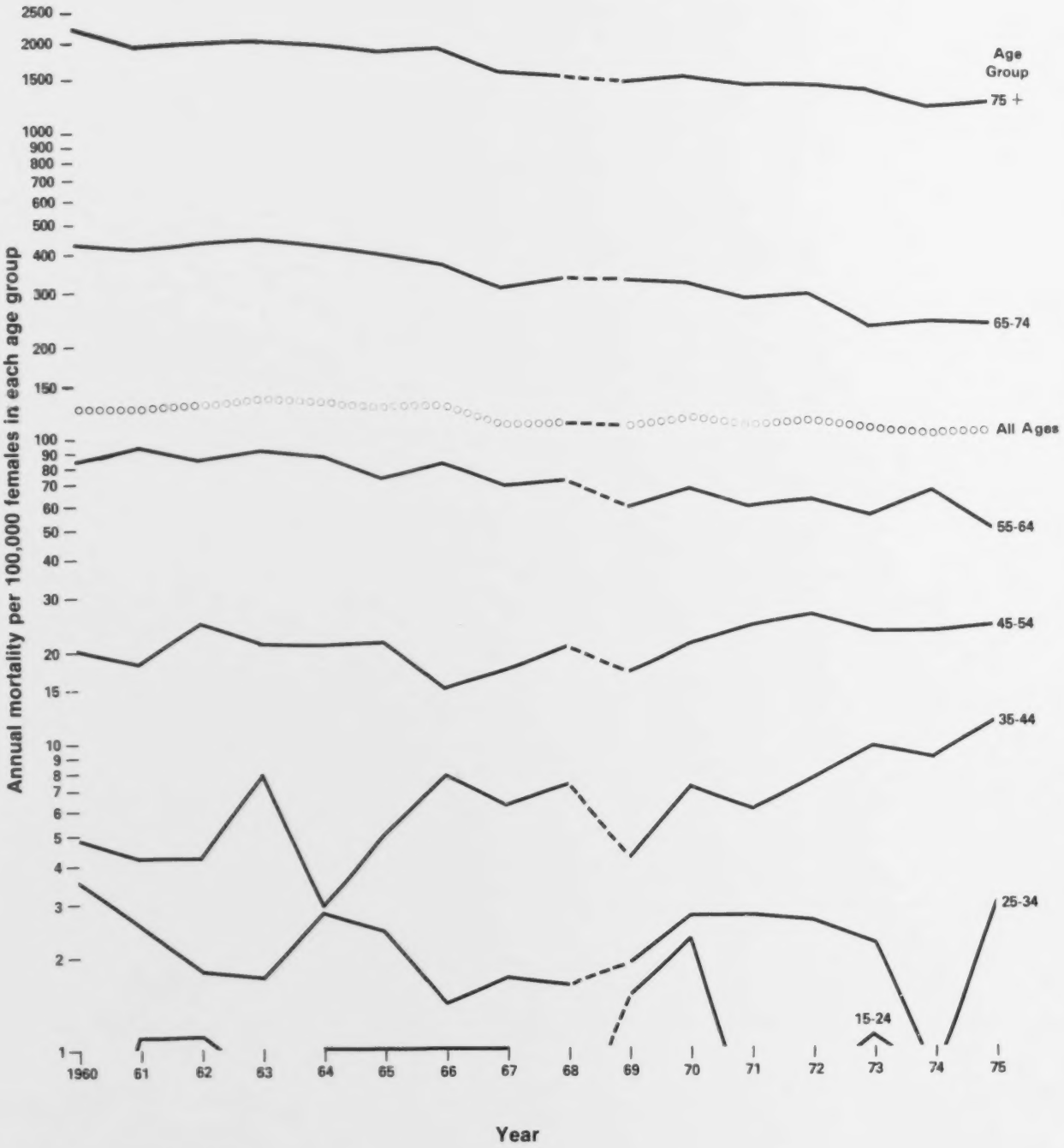


Mortality rates for cerebrovascular disease remained steady for females of reproductive age in England and Wales, while slight declines are evident in the 55-74 age groups.

*ICD 430-438 (1968-1974); ICD 330-334 (1960-1967)

Source: Ravenholt and Rinehart (155) based on data from WHO (202)

Figure 12. Mortality from Cerebrovascular Disease,* Females, Aged 15 and Older, by 10-Year Age Groups, Denmark, 1960–1975



Mortality rates for cerebrovascular disease for females over age 54 have generally decreased, but for females aged 35–54 an increase occurred during the last decade.

*ICD 430–438 (1969–1975); ICD 330–334 (1960–1968)

Source: Ravenholt and Rinehart (155) based on data from US National Center for Health Statistics (207)

1968—perhaps due to reduced fertility—while rates for men remained constant (34).

While analysis of vital statistics trends can be hindered by the quality of the data and the difficulty of taking into account other relevant trends, the data raise legitimate questions about the applicability of risk estimates from British women to other populations, even those in developed countries like the United States. It is possible that substantially higher risks among specific, relatively small subgroups—for example, women over age 35 who smoke or who have multiple predisposing factors—may affect the results of case-comparison and cohort studies without making a detectable difference in national death rates. Further research on smoking and other characteristics of oral contraceptive users who develop circulatory system diseases, including attention to other factors that might predispose them to such diseases, would be helpful.

A study which found a correlation between vital statistics and OC use data—and, in fact, estimated on that basis a relative risk of death from circulatory system disease similar to that later reported by the Royal College study (169)—was published in 1976 (21). V. Beral compared mortality rates from 21 countries, most of them European, for 1961–1962 and 1971–1972. The percentage change in mortality rates for women aged 15–44 tended to be highest in countries where pill use was highest in 1971–1972. Similar correlations of percentage change in pill use with percentage change in mortality rates could not be found for older women or for men between 1961–1962 and 1971–1972 or for women of reproductive age between the pre-pill years 1955–1956 and 1961–1962.

Recent analysis of mortality and OC use trends in the same 21 countries challenges Beral's conclusions. Researchers M. Belsey, Y. Russell, and K. Kinnear at the World Health Organization compared mortality trends in two periods—first, the period between 1955 and the year in which each country reached one-third of peak OC use and, second, the years of peak use thereafter, usually from the mid- or late-1960s to 1973–1976, depending on the availability of recent data for each country. This reduced the possible impact of the wide annual variations in mortality rates, characteristic of uncommon diseases in small populations, that could affect a comparison of rates in two short, separate periods. Also, they divided the populations into three ten-year age groups (19).

The analysis failed to show an association between trends in total cardiovascular disease mortality rates and the level of use of oral contraceptive hormonal steroids in age groups 15–24 and 25–34. On the other hand, in age group 35–44 it showed an improvement in mortality trends in association with oral contraceptive use; that is, the decline in cardiovascular mortality among older women accelerated as pill use increased. Moreover, the countries which did show adverse changes associated with pill use were among those with less than half the median prevalence of pill use for all 21 countries.

The researchers found that for all ages falling mortality from cardiovascular disease was correlated with decreasing per capita consumption of fats and oils, based on UN Food and Agriculture Organization data. In other words, these diet changes had a greater effect on the incidence of cardiovascular disease than did oral contraceptive use. Belsey and colleagues suggest that vital statistics data are "not suitable for testing the association between cardiovascular disease and oral contraceptive use" (19). However, in this case the questions raised by these data deserve further attention and research.

SMOKING, OCS, AND CIRCULATORY SYSTEM DISEASES

Smoking by itself increases the risk of many circulatory system diseases for all women, regardless of their contraceptive method (11, 41, 85, 94, 118, 133). Moreover, the risk rises with the number of cigarettes smoked daily. Thus the woman using oral contraceptives might in any case want to avoid adding to her risk by smoking. More importantly, however, smoking and oral contraceptives together have a synergistic effect on the occurrence of some circulatory system diseases, that is, an effect greater than the sum of their two separate effects. Heart attack and hemorrhagic stroke, particularly subarachnoid hemorrhage, show the synergistic effect most clearly.

The first evidence for the importance of smoking in circulatory system diseases in OC users came from a late 1960s British case-comparison study of thromboembolic disease (211, 212), as reanalyzed by H. Frederiksen and R.T. Ravenholt (61, 62). Frederiksen and Ravenholt pointed out that the relative incidence of thromboembolism was almost 23 times higher in OC users who smoked heavily than in those who neither smoked nor used OCs, while it was about seven times higher in OC users who did not smoke (62) (see Table 19). Subsequent research has associated smoking and venous thromboembolism (145) but has not confirmed a synergistic effect of smoking and OC use on the occurrence of the disease (107, 145, 170).

In circulatory system disease generally, the crucial role of smoking is clear in the Royal College study (169). The death rate for women who both smoked and used OCs was three to four times greater than for nonsmoking OC users or smokers who did not use OCs (see Table 20). Among smokers, the difference in mortality rates between OC users and nonusers was statistically significant ($p<0.01$). Among nonsmokers, a difference was observed but, with only seven deaths among nonsmokers, it lacked statistical significance. In the Oxford/FPA study, seven of the nine OC users who died of cardiovascular disease were smokers (215).

Table 19. Relative Incidence Rates of Thromboembolism, by History of Cigarette Smoking and Use of Oral Contraception, in a British Case-Comparison Study, as Reanalyzed by Frederiksen and Ravenholt, 1970

OC/Smoking Status	Relative Incidence Rate
No smoking, no OCs	1
Smoking 15+ cigarettes a day, no OCs	1.5 × 1
OCs, no smoking	7.2 × 1
OCs, smoking 15+ cigarettes a day	22.7 × 1

Source: Frederiksen and Ravenholt (62)

Since the data released from these studies so far do not divide the women who smoked either by age or by their status as past or ever smokers or as light or heavy smokers, it is possible that the overall impact of smoking is even greater than currently available figures suggest.

The recent Walnut Creek study of subarachnoid hemorrhage found a strong relationship between smoking and this type of stroke and also a dramatic synergism of smoking and oral contraceptive use. Regardless of their contraceptive status, women hospitalized for subarachnoid hemorrhage had a relative risk of smoking at entry into the study of 5.7. For OC users, the relative risk was 6.5. But for smokers who also used OCs, the relative risk was 21.9. In fact, there were only 3 nonsmokers among the 11 cases—too few to study separately (144).

An earlier study of 196 hemorrhagic strokes in US women showed greater hazards for smokers than for OC users and some evidence of synergism. For nonsmokers, the increase in risk associated with pill use was very slight—20 percent—and not statistically significant. On the other hand, smoking, in the absence of OC use, approximately doubled the risk of hemorrhagic stroke. But for OC users who smoked a pack of cigarettes or more a day, the relative risk jumped to 6.1 or 7.6 compared with that of similar smokers in two control groups. Synergism of OC use and smoking was not observed for thrombotic stroke, nor was smoking a risk factor independently (41).

Table 20. Rates of Mortality from Nonrheumatic Circulatory System Diseases in the Royal College of General Practitioners' Cohort Study

OC/smoking status*	Deaths/100,000 woman-years**
No smoking, no OCs	3.0 (2 deaths)
Smoking, no OCs	8.9 (3 deaths)
OCs, no smoking	13.8 (5 deaths)
OCs and smoking	39.5 (19 deaths)

*Smoking status—at date of admission to study; OC status—at any time during study.
**Rates standardized for age at entry, social class, and parity.

Source: Royal College of General Practitioners' Oral Contraception Study (169)

Data on heart attack from British and US case-comparison studies reveal a powerful synergism of smoking and oral contraceptive use at work in the occurrence of this disease, too. The effect is so strong that it led one group of US researchers to conclude that ". . . acute MI [myocardial infarction] in otherwise healthy premenopausal women is almost exclusively an illness of cigarette smokers" (94). As reanalyzed by H.W. Ory (135), the data from Britain (118) show that nonsmokers who have used OCs approximately doubled their risk of heart attack, but the difference was not statistically significant; there were only 16 cases of heart attack in women who had never smoked, compared with 41 cases in current smokers. Adding smoking to OC use, however, multiplied the danger fivefold, to a relative risk of 11. Smoking cigarettes heavily—25 or more a day—was more likely to lead to heart attack than was oral contraceptive use (135).

Table 21. Estimated Annual Mortality Rate per 100,000 Women from Myocardial Infarction, by Use of Oral Contraceptives, Smoking Habits, and Age

Smoking Habit	Women aged 30–39		Women aged 40–44	
	OC Users	Nonusers	OC Users	Nonusers
All Smokers	10.2	2.6	62.0	15.9
Heavy	13.0	5.1	78.7	31.3
Light	4.7	0.9	28.6	5.7
Nonsmokers	1.8	1.2	10.7	7.4

Source: Jain (89)

Using data from the British studies, A.K. Jain has estimated annual mortality from heart attack in OC users and nonusers according to their smoking habits and age. The effects of the combination of age, smoking, and OC use are clear (89) (see Table 21).

A recent US study of 26 nonfatal heart attack cases and 59 controls found the same synergism of smoking and OC use. OC use alone and smoking alone had virtually no effect on risk of heart attack, but smoking and OC use together produced a relative risk of almost 31 (see Table 22). Only two of the 26 cases were nonsmokers. The researchers estimated the risks to nonsmokers to be "extremely small" (94).

Young women likely to suffer heart attacks are also likely to have high cholesterol levels in the blood, hypertension, a history of preeclamptic toxemia during pregnancy, a tendency to obesity and/or to be smokers (118). These are generally recognized risk factors for myocardial infarction. Ory points out that only 1 of 58 survivors of heart attack studied by J.I. Mann and colleagues used OCs and had no other risk factors. Thus the risk estimates derived from the study apply only to OC users with at least one other risk factor (135). For these women, who, according to Mann and colleagues' data, may constitute one-third of the women of reproductive age in a developed country (118), OC use may multiply their risk of heart attack—already greater than for women without other risk factors—by 2.8 (135).

The biochemical mechanisms by which smoking and oral contraceptive use interact are not yet known. Recent work shows that smoking lowers HDL cholesterol levels, with

Table 22. Smoking and Oral Contraceptive Use in a US Case-Comparison Study of Myocardial Infarction

OC/Smoking Status*	Number (Percentage)		Relative Risk
	Cases	Controls	
No smoking, no OCs	—	28 (47)	—
OCs, no smoking	2 (8)	10 (17)	0.4
Smoking, no OCs	6 (23)	17 (29)	0.7
OCs and smoking	18 (69)	4 (7)	30.9
Total	26 (100)	59 (100)	

*Smoking—at time of hospital admission; OC use—within three months before hospital admission.

Source: Jick et al. (94)

lower levels for heavier smoking, thus perhaps raising the risk of heart attack (10, 30). The effects of OCs and smoking appear to be additive rather than multiplicative. As the researchers point out, this does not rule out a synergistic effect on disease incidence, because heart attack risk may not be linearly related to HDL cholesterol level (30).

Further research may help explain the synergistic action of smoking and oral contraceptives, better identify the diseases involved, and better quantify the risks of the two factors separately and in combination. It is clear already, however, that the risks of heart attack and subarachnoid hemorrhage for healthy young OC users who do not smoke or have no other factors predisposing them to cardiovascular disease are very slight.

In Developing Countries

Applying the findings of US and British epidemiologic studies directly to women in developing countries may not be justified. The women of developing countries differ from the women of industrialized nations in diet, lifestyle, genetic heritage, exposure to disease vectors and environmental contaminants, smoking habits, and myriad other ways that seem to affect cardiovascular disease. Furthermore, not enough research has been done in developing countries to justify a conclusion that the risk factors for cardiovascular diseases that have been identified in the industrialized nations are important elsewhere. Indeed, some have observed that they are not. For example, A.G. Shaper notes that:

> It is the experience of the vast majority of clinicians and pathologists working in the tropics that even the obese, sedentary, severely hypertensive, long-standing diabetic does not (except with the rarest of exceptions) develop coronary heart disease, even in soft-water areas (183).

Furthermore, it is widely recognized that in developing countries (1) the incidence of circulatory system diseases is low, with the possible exception of hypertension, and (2) many "Western" risk factors are far less prevalent. This double advantage would mean that, even if US and British risk ratios could be applied to developing country women, the incidence of circulatory system disease attributable to OCs would be very slight.

While a few areas are exceptions, heart attack is uncommon in developing countries (183, 184, 195, 210). Venous thromboembolic disease also appears to be rare (37, 38, 193, 195). Hypertension seems to be less common in traditional societies (210, 219). In some groups blood pressure does not rise with age and high blood pressure is almost nonexistent (139, 182, 219). Blood pressure tends to be higher in urban than in rural areas and to rise in those who move from the country to the city (125, 182, 219).

Smoking among women is, generally, a practice of the developed countries. National per capita tobacco consumption corresponds to per capita income (140), and in the developing countries women usually comprise a much smaller portion of smokers and of those who smoke heavily than they do in the developed countries. A sampling of data from around the world discloses these percentages of women smoking: 4–6 percent in Guyana (12, 122), 1.6 percent in Sri Lanka (209), 3.6 and 7.8 percent in two ethnic groups in Natal (179), 13.9 percent in Jamaica (122), and, in Latin American cities, from 7 percent in Lima to 26 percent in Santiago (96). This compares with 30 to 50 percent in the US and Britain (122, 167, 208). Thus whatever effect smoking may have on the health of OC users in developing countries, it would be a much smaller public health problem than in the developed countries.

Assuming that the US and British risk factors for heart attack of smoking, high cholesterol levels, and hypertension apply in developing countries, J. Heiby has used data from British studies (114, 134, 214) to estimate the risk of heart attack for women in traditional societies. Like smoking among women, hypercholesterolemia is relatively rare in traditional societies (12, 113, 137, 139, 180), while hypertension rates Heiby assumed to be similar. Heiby calculated, then, that the proportion of women in a traditional society with one of these risk factors would be 30 percent that of British women; with two risk factors, 9 percent; with three risk factors, 1.5 percent. Overall, the mortality rate—presuming equal survival rates for heart attack cases—would be 19 percent of the British rate, or roughly four heart attack deaths annually per one million OC users. Screening out tobacco users, Heiby estimated, would reduce the rate to three per million (74).

Heiby's estimate deals only with heart attack risk. Given the need to rely on crude assumptions about the role of risk factors and sparse data on their prevalence, it is a rough estimate, not applicable to any specific country or group of women. Nonetheless, it suggests the considerably lower risk of circulatory system disease in women, including those who use oral contraceptives, in developing countries compared with women in developed countries. Only actual research in developing countries will determine whether the risks exist there and to what extent.

NEOPLASIA

When, in May 1977, research on oral contraceptives and neoplasia was reviewed in **Population Reports** A–4 and Supplement, there was no clear evidence that combined oral contraceptives cause cancer. Substantial evidence did exist, however, that users of oral contraceptives develop benign breast neoplasia less frequently than do nonusers, and that they develop a rare, benign, although sometimes life-threatening, liver tumor more often than do nonusers. Findings reported in the last 18 months have not altered those conclusions.

Biologically, the relationship between steroidal contraceptives and malignant disease, especially cancer of the breast and reproductive system, must rank as the single most important concern in relation to long-term use of oral contraceptives. The development and course of several tumors of the reproductive system are modified by the level of circulating hormones. The relationship is a complicated one, and different hormones in different concentrations can have either an adverse effect, a beneficial effect, or no effect whatsoever, depending on the type of tumor, the organ involved, and the woman's reproductive history.

In the USA about one-quarter of all women die of cancer and one-quarter of those die of breast cancer. The disease kills one in 20 women in Britain and one in 18 in the USA, where it is the largest single cause of death among women aged 40–44 (6). It is common in nearly all developed countries but less common in

developing countries. Breast cancer is so common in industrialized nations, in fact, that any change in frequency which might be induced by steroidal contraceptives would be profoundly significant. Fortunately, after two decades of extensive OC use, the evidence, including a study published since the last survey in **Population Reports**, weighs against an association of OCs with breast cancer.

In recent studies the protective effect of OCs against benign breast disease has been confirmed and better defined. New information on cervical lesions has raised suspicions somewhat but is ambiguous. A single small study has suggested that OC users may be less likely to develop ovarian cancer than are nonusers, while another, also unconfirmed, investigates links between OC use and melanoma.

Breast Cancer

In the Royal College study, 14 of the women who had ever used orals died of cancer compared with 20 of the never users. Among the OC users, cancers of the reproductive system included three breast cancers and one cancer of the cervix; among the never users, or controls, there were six deaths from breast cancer, three from cancer of the ovary, and one from cancer of the vulva. In the Oxford study 12 women using diaphragms or IUDs died of cancer compared with 10 OC users. (See Table 11.) In neither study were the differences statistically significant, however, and women with a previous history of breast disease may have been encouraged not to use orals. Nevertheless, the lower number of cancer deaths among OC users is reassuring.

Although the neoplasia deaths are not discussed in the brief 1977 reports, an earlier article by M. Vessey and colleagues (213) on morbidity in the Oxford/FPA group reported that OC users were about half as likely to develop cancer as diaphragm and IUD users and also about half as likely to develop breast cancer specifically, although the number of women suffering from breast cancer was too small to calculate a statistically significant difference.

Like most earlier studies (see **Population Reports** A–4), the only epidemiologic study specifically on breast cancer and oral contraceptive use to appear in the last 18 months found no association between the two (99). J.L. Kelsey and colleagues, looking at 99 cases of cancer and an equal number of matched controls, found 23 pairs in which the case used OCs but the control did not and 17 pairs where the situation was reversed. After adjustment for other possibly relevant differences between cases and controls, the relative risk of OC use was estimated to be 1.6, not a statistically significant difference. Evidence against a cause-and-effect association included the lack of any relationships of cancer to duration of OC use, to age at first use, or to length of time since first use. Also, Kelsey and colleagues found no evidence to support the findings of an earlier California study that risk of developing breast cancer was increased for OC users who had taken the pill for more than two but less than four years or who had had benign breast disease (53, 138). The number of cases examined in the recent study was not as large as in the earlier one, however. Not tested was the earlier study's finding of more OC use among cases who used the pill before the birth of their first child than among their controls.

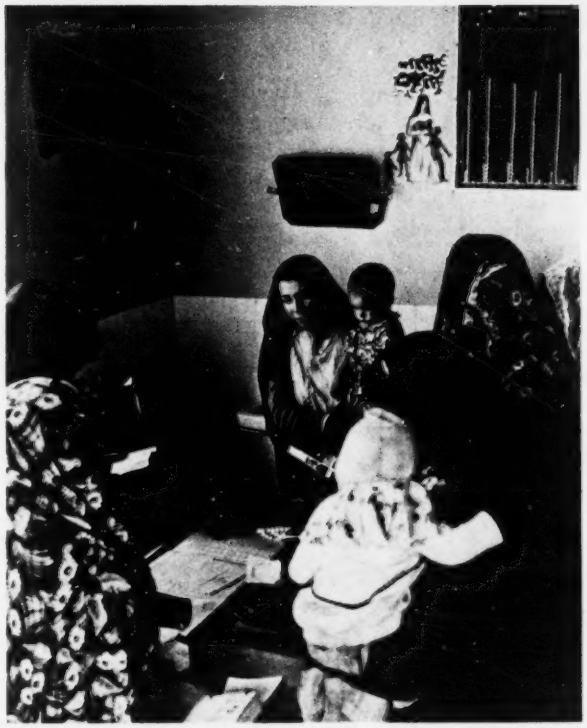


Figure 13. A particular feature of the distribution of pills at the Shiraz Family Center of Iran is the reclaiming of used wrappings before new supplies are provided. (WHO/Zeppilli)

Corollary evidence against a role of oral contraceptives in breast cancer comes from a recent study of breast cancer tissue from 44 OC users and from an equal number of nonusers of similar age and parity (188). Researchers could find no differences between the two groups in the histological features of the tissue or in the extent to which the malignancy had spread to axillary lymph nodes. In fact, cancer recurred significantly more often in nonusers with axillary lymph node involvement than in OCs users whose disease had reached a similar stage. An observation like this underscores the comment that, despite extensive research, the role of hormones in breast cancer is still far from clear (100).

Benign Breast Disease

The protective effect of oral contraceptives against benign breast neoplasia is the clearest of relationships between OCs and neoplastic diseases. Recent months have added two more studies to those affirming this beneficial association (see **Population Reports** A–4).

J.L. Kelsey and colleagues found that women with the two most common types of benign breast neoplasia, cystic hyperplasia (n=209) and fibroadenoma (n=120), had used oral contraceptives for shorter periods of time than their individually matched controls. This confirmed earlier studies. Four years or more of OC use halved the risk of developing benign breast disease. Unexpectedly, further analysis showed that only sequential oral contraceptives—and not the more widely used combined type—seemed to manifest this protective effect. An effect limited to sequentials had not been suggested by previous studies (99).

A Boston (USA) study based on questionnaires completed by 65,843 women in 1970 showed that hospitalizations for benign breast disease in 1969 decreased with the duration of OC use. Hospitalization rates for women with 1–15 months of OC use were similar to those for never users, but for over 15 months of use showed a clear reduction in rate. Among nonusers, the rate was 5.4 per 1,000 women per year; for 1–9 months of OC use, 6.4; for 10–15 months, 6.0; for 16–39 months, 3.1; and for more than 39 months, 3.1 (79).

Women who develop benign breast disease have a propensity to develop breast cancer later. But in OC users no protective effect against breast cancer, comparable to the effect against benign disease, has yet been observed. Tissue studies conducted at Yale University in conjunction with the epidemiologic study of breast neoplasia by Kelsey and colleagues suggest an explanation for this paradox (110). Examining tissue samples from fibrocystic breast tumors in 205 women, V. LiVolsi and colleagues found that OC use was associated with a smaller number only of benign tumors in which there was little or no atypical ductal epithelial cell development. The greater the degree of atypical epithelial cell development, previous research on fibrocystic disease has shown, the greater the chance that cancer will follow. The researchers suspect that fibrocystic diseases with varying degrees of atypia are different stages of the same disease. If so, more needs to be learned about what influences progression from one stage to another before the role of the pill can be thoroughly explained.

Ovarian Cancer

A recent case-comparison study from Britain suggests that oral contraceptives may protect their users against ovarian cancer. The number of OC users in the study was small, however, and potential confounding factors were not taken into account. In all, 300 cases of ovarian cancer were compared with two sets of controls individually matched for age—one set consisting of women in hospitals for gynecological complaints other than ovarian tumors or cysts; the other, women from the same neighborhoods as the cases. Only 19 of the cases, compared with 31 of each of the control groups, had used oral contraceptives. Compared with the hospital controls, the relative risk of previous pill use among the cases was 0.59; compared with the neighborhood controls, 0.33, the latter being statistically significant ($p<0.05$) (128). The study is the first on ovarian cancer and OCs, and its findings are an impetus to further inquiry. In the Royal College mortality study there were three deaths from ovarian cancer among the never users but none among the users (169); in the Oxford/FPA study, one OC user and one IUD user developed ovarian cancer (213). An association of rising rates of ovarian cancer with declining parity (22), coupled with the case-comparison report on OCs, suggests that interruption of ovulation may reduce the risk of ovarian cancer.

Cervical Neoplasia

Age at first intercourse and the number of sexual contacts are key determinants of the occurrence of cancer of the cervix (16, 120, 165). The only study to analyze thoroughly the relationship among OCs, sexual behavior, and cervical malignancy—the Walnut Creek study—is now finding that sexual behavior accounts for some but not all of the apparently higher risk of cervical neoplasia among OC users.

The Walnut Creek researchers found initially that the incidence of cervical carcinoma in situ, but not of dysplasia, thought to be its sometimes reversible precursor, was related to duration of oral contraceptive use. Their analysis was based on 35 cases of carcinoma in situ and 31 of dysplasia found among the 14,567 women in the Walnut Creek study population (143). Subsequently, when account was taken of early sexual activity and number of partners, the difference in risk between users and nonusers diminished, losing its statistical significance, and the association with duration of use was weakened (148, 201). Additional data from the Walnut Creek study will be published soon.

J.G. Boyce and colleagues in New York City looked at 689 women with cervical carcinoma in situ and an equal number of controls without the disease, matched for several variables, including age at first coitus. Similar proportions of the case and control groups had used oral contraceptives, and no differences between the groups appeared with regard to duration of use, estrogen dose, or the year in which OCs were used (28).

Other recent reports have not analyzed differences in sexual behavior. Their results vary. The Oxford/FPA study reported virtually equal rates of carcinoma in situ developing in OC and IUD users—0.45 and 0.43 per 1,000 women-years respectively—but no cases occurred in diaphragm users, suggesting a protective effect of this barrier method of contraception (213). The Boston mail survey found that OC users were hospitalized for cancer of the cervix five times more often than nonusers in 1969 but only 1.8 times more often in 1970–1972. The researchers suggested that the higher rates for OC users might be due to doctors' tendency to recommend hospitalization more frequently for OC users generally (79).

A mass screening of women in the Netherlands disclosed no statistically significant difference in the prevalence of cervical malignancy between OC users and nonusers. After adjustment for age differences, OC users were 1.2 times more likely to have cervical carcinoma or invasive cancer than were nonusers (42) (see Table 23).

A long-term study of US women with dysplasia, some of whom had chosen the pill, some, other methods of contraception, has suggested that dysplasia was more likely to progress to carcinoma in situ in the pill users (191). The difference appeared only after more than five years of followup and became statistically significant after more

Table 23. Prevalence (and Crude Prevalence Rate per 1,000 Women) of Cervical Malignancy in a Netherlands Cervical Cytology Screening Program, 1970–1973

	OC Users	Nonusers
Number screened	9,023	19,500
Ca in situ*	33 (5.8)	73 (3.7)
Invasive ca*	7 (0.8)	25 (1.3)
All carcinomas of cervix	40 (4.4)	98 (5.0)

*Histological diagnosis

Source: Collette et al. (42)

than six years. The numbers involved are small due to a high dropout rate. Looking at the data another way, researchers observed that an index of the severity of dysplasia, averaged for each group, declined for nonusers over a 4-year period but stayed approximately the same for users. In contrast to these findings, a sample of 300 women with normal cervical cytology, chosen from the same population of clients of Los Angeles family planning clinics, has showed no differences related to contraceptive method in the development of atypical cytology. Together these findings could be interpreted as reflecting a role for oral contraceptives in promoting but not initiating cervical neoplasia, but more research will be needed before conclusions can be reached.

Liver Tumors

A rare type of benign liver tumor, known as hepatocellular adenoma or liver cell adenoma, is associated with long-term OC use, especially in older women (9, 55, 103; see also **Population Reports** A-4, p. A88-A90). The actual incidence of the tumor is unknown; 500 cases have been reported in the USA, not all of them in pill users (9). A recent case-comparison study shows that the effect of duration of use on the risk of developing hepatocellular adenoma is marked. When compared with women who had used OCs for one year or less, 4-year users faced nine times the risk; 4-7 year users, 120 times the risk, and 8-year or longer users, 500 times the risk (9). While the relative risk is dramatic, the rarity of the disease keeps its incidence in pill users low. A WHO Scientific Group studying oral contraceptives and neoplasia estimated the increase in incidence attributable to oral contraceptives to be no more than 3 per 100,000 women per year for those under age 30 and some unknown figure "certainly greater than 3 per 100,000" for older women (201). Hepatocellular adenomas seem to be most closely associated with the high-dose OCs, which have been used less frequently in recent years (9).

Most cases of hepatocellular adenoma are detected when a patient complains of pain in the abdomen and of feeling a mass in the upper right quadrant. These tumors can rupture, causing bleeding into the peritoneum, which in turn produces acute pain and leads to circulatory collapse and sometimes death (162). The usual treatment for adenomas is resection (55). In some cases, however, withdrawal of OCs has led to regression of the tumor (47, 151).

Melanoma

Researchers at Walnut Creek found that melanoma occurred slightly more frequently in users of oral contraceptives than in nonusers. Their findings were not statistically significant, and they could not rule out the possibility that their results were due to differences in exposure to the sun rather than to oral contraceptive use. In about 90,000 woman-years of observation of the nearly 18,000 participants in the study, 22 cases of malignant melanoma were diagnosed. Adjusted for age differences, the number of cases per 100,000 woman-years was 17.6 for women aged 25-54 who had never used OCs (five cases), 24.1 for women who had used OCs for less than four years (eight cases), and 29.5 for women who had used the pill for longer periods (six cases). (Three women had used estrogens other than oral contraceptives.) Considered by ten-year age groups, similar trends appeared in the oldest and youngest groups but not in the 35-44 age group. The number of cases is small and none of these differences is statistically significant. The same researchers conducted a case-comparison study as well, using 37 other cases and twice as many controls. Their estimate of relative risk was 1.8, not statistically significant (24).

Endocrine factors appear to be involved in melanoma in some way (59, 174), but a major risk factor apparently is exposure to sunlight (54). This was not taken into account in the Walnut Creek study. Another case-comparison study of the issue now beginning in California will look at a variety of possible risk factors in addition to oral contraceptive use.

OTHER CONDITIONS

Since the summary of oral contraceptive research in **Population Reports** A-2 of March 1975, information emerging from many different studies—the ongoing cohort studies and specific case-comparison and laboratory studies—has revealed little outside the realm of circulatory system disease that substantially changes previous assessments of oral contraceptive safety and benefits. Among long-standing concerns about oral contraceptives have been questions about the return of fecundity after their use and about congenital malformations in offspring of former OC users. New information from large-scale studies is reassuring on both counts. In contrast to this long-sought information, recent cohort study findings on rheumatoid arthritis and acute hepatitis are unexpected: OC users were diagnosed less frequently than nonusers as having rheumatoid arthritis and more frequently as having hepatitis.

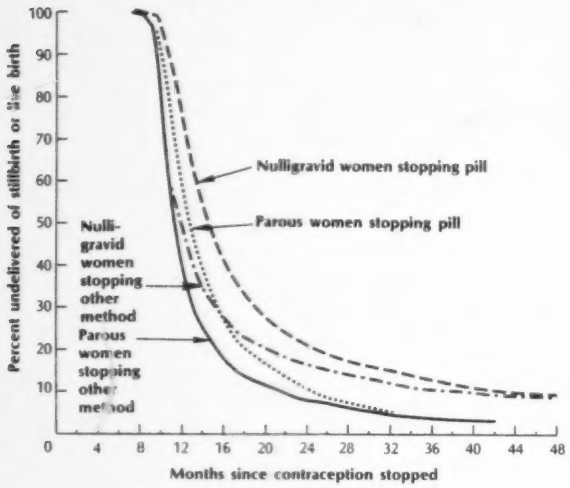
Return of Fecundity

Women who stop taking oral contraceptives to become pregnant can expect to wait a few months longer for conception than former users of IUDs and traditional methods, but there seems to be little risk that oral contraceptive use leads to permanent sterility. The best data come from the Oxford/FPA study and the Jerusalem Perinatal Study. They compare the conception rates over time of large numbers of women—1,174 former pill users and 779 former users of other methods in the Oxford/FPA study, 1,403 pill users and 4,477 users of other methods in the Jerusalem study (73, 218). Both studies found that conception rates among former pill users lagged behind rates among other women for a few months but eventually caught up. In the Jerusalem study the difference disappeared in three months; in the Oxford/FPA study, in 42 months (see Figure 14). Duration of OC use did not appear to affect the length of temporary impairment of fertility in the Oxford study (218). In the Jerusalem study, fertility returned more slowly on the average to older pill users, particularly if they had used the pill for a long time. There was little suppression of fertility in young women, regardless of the length of pill use, or in older, short-term users (73).

Effects On Offspring

Recent large-scale studies have dispelled much of the fear that women who have used oral contraceptives **before** pregnancy might be more likely than nonusers to bear

Figure 14. Fertility after Stopping Different Methods of Contraception in Order to Conceive, Oxford/ Family Planning Association Study



Source: Vessey et al. (218)

infants with congenital malformations. At the same time, while there is still much to be learned, research strongly suggests that women should avoid taking any steroidal hormones **during** pregnancy and should switch to another contraceptive method immediately if they think they might be pregnant.

Both British cohort studies and the Boston area mail survey have found no evidence of any major adverse impact of previous pill use on fetal development (164, 171, 213). These studies involved from over 1,000 to more than 5,000 births to former pill users. In none of them did the overall rate of malformations differ significantly between former pill users and nonusers nor did any specific type of malformation show an association with previous pill use (see Table 24*). No effect—or else a slight beneficial effect—of pill use on rates of miscarriage has been observed in these studies (162, 171, 218).

In general, a study of about 3,000 pill users and over 13,500 nonusers who gave birth in Jerusalem over a two-year period produced similar reassuring results. Congenital malformations as a whole and most major malformations were less frequent among the infants born to women who had used the pill since their previous pregnancy (if any). The former pill users' babies were heavier, partly due to longer intervals between births, and perinatal mortality was generally lower. Rates of previous miscarriage were higher, however. Also, Down's syndrome was more frequent in pill users' offspring, but the number of cases was small—10 in users and 24 in nonusers—and the difference not statistically significant (73). Contrary to the Jerusalem report, a US case-comparison study, involving 103 women whose children had Down's syndrome and an equal number of women of similar age, date of delivery, and area of residence who had normal children, found OC use before pregnancy more common in the mothers of normal children. The difference did not quite reach statistical significance (91).

*Table 24, which summarizes selected cohort studies of birth defects and oral contraceptive use, appears on p. A-183.

Two recent case-comparison studies confirm the general findings of cohort studies that there is no link between OC use **before** pregnancy and congenital malformation. In a Connecticut (USA) study, 1,370 cases with congenital malformations were compared with 2,968 normal infants. The cases' mothers were slightly less likely to have used OCs in the year before conception than were the controls'. The difference was not statistically significant. Down's syndrome was not associated with OC use, nor was any other of 16 types of defects (29). Another US study found that OC use in the year before conception was approximately 25 percent both among the mothers of 607 infants with congential malformations and among the mothers of an equal number of normal infants (92).

The information on OC use **during** pregnancy, as opposed to **before** pregnancy, suggests some danger of certain types of malformations. Studies have associated congenital malformations with large doses of hormones given during pregnancy as pregnancy tests or to prevent miscarriage. This has led researchers to look at oral contraceptives specifically, and several small case-comparison studies have associated inadvertent use of OCs during pregnancy with certain types of birth defects—in particular, limb reduction, heart defects, and a syndrome of multiple malformations of vertebrae, anus, heart, trachea, esophagus, kidneys, and limbs (93, 130, 131). On the other hand, hypospadias, a condition which may be due to fetal hormonal disorders and which has been linked to large doses of progestins taken during pregnancy (3), has not been noted particularly in infants exposed in utero to OC hormones.

Two recent reports reinforce earlier findings that heart defects can result from use of hormones during pregnancy, but the proportion of OC users among the hormone users has been small. Six children with cardiovascular defects were born to 278 women who had used OCs during early pregnancy (21.5 per 1,000), compared with 385 in 49,240 births to women who did not (7.8 per 1,000). Although this difference involving OCs is not statistically significant, exposure during pregnancy to female hormones in general was significantly associated with cardiovascular malformations (75) (see Table 24). A case-comparison study of congenital heart disease produced a similar result—a significant difference when all hormones were considered but not for oral contraceptives separately (90).

In the Connecticut case-comparison study, OC use **during** pregnancy was slightly more common in the cases' mothers than in the controls', but not significantly so. For a number of specific malformations, including Down's syndrome and anacephaly, OC use was twice as frequent in cases' mothers as in controls', but again the difference lacked statistical significance (29).

The unexpected findings of the Connecticut study are that (1) heavy smoking (more than 20 cigarettes a day) was significantly more common in the cases' mothers than in the controls', and (2) heavy smoking and oral contraceptive use during pregnancy appeared to act synergistically. The researchers calculated that those who smoked heavily and had used OCs **during** pregnancy faced 13 times the risk of having a child with a congenital malformation that nonsmokers who had not used OCs did. While statistically significant, this estimate has a wide margin of error because the numbers involved are small—six cases and one control

had mothers who both had used OCs during pregnancy and smoked heavily.

Although an association between congenital defects and the specific use of OCs **during** pregnancy has not been established conclusively (5, 129), avoiding the use of all hormones, including oral contraceptives, seems a reasonable precaution for a pregnant woman.

Rheumatoid Arthritis

Oral contraceptives may protect their users against rheumatoid arthritis. The disease occurred approximately half as frequently in OC users as in nonusers in the Royal College study, according to a recent report (172) (see Table 25). Ordinarily, the incidence of arthritis rises with age, but among Royal College OC users it did not. The protective effect lasted only while the women used OCs, and researchers could find no relationship with dose or duration of observation. In absolute terms, the effect would benefit perhaps 33 per 100,000 OC users per year.

A study of 25-year incidence trends in a US community supports the Royal College finding. While the incidence of first diagnoses of rheumatoid arthritis rose for both men and women in the period from 1950 to 1965, the rate for women fell rapidly after 1965, as oral contraceptive use in the USA increased rapidly; during the same period the rate for men leveled off (109) (see Figure 15).

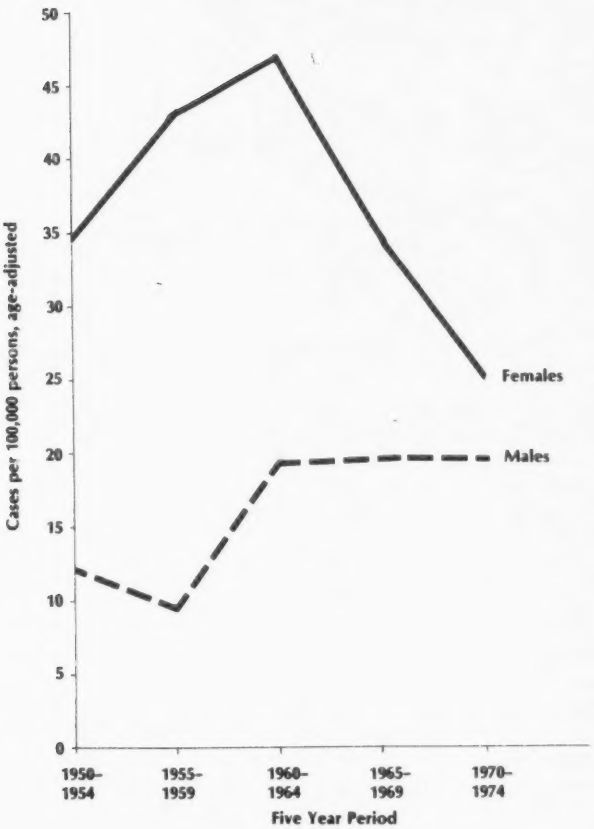
Table 25. Rheumatoid Arthritis and Use of Oral Contraceptives in the Royal College of General Practitioners' Oral Contraception Study

	Users	Former users	Non-users
Length of observation (woman-years)	60,607	36,008	100,047
No. of cases	18	19	57
Rate (per 1,000 woman-years)*	0.31	0.53	0.63
Ratio of rates (compared with nonusers)	0.49**	0.84	1.0

*Standardized for age, parity, smoking, and social class
**$p<0.01$

Source: Royal College of General Practitioners' Oral Contraception Study (172)

Figure 15. Age-adjusted Rates of Rheumatoid Arthritis in the Population of Rochester, Minnesota, USA, 1950–1974



Source: Linos et al. (109)

Earlier studies, all of them small, of oral contraceptive use and rheumatoid arthritis had produced conflicting results (26, 65, 194). The Walnut Creek study, contrary to earlier, small studies (26, 98), found that the prevalence of rheumatoid factor in the blood was lower in OC users than in nonusers, but not significantly so (189). Royal College researchers point out that pregnancy sometimes relieves the symptoms of rheumatoid arthritis; they postulate that suppression of autoimmune response by hormones may explain the protective effect both of OC use and of pregnancy (172).

Acute Hepatitis

Results from the Boston Collaborative Drug Surveillance Program suggest that users of oral contraceptives, especially young women, are more likely to be diagnosed as having acute hepatitis than are nonusers. The researchers found 68 cases of hepatitis and compared them with 1,142 women in the same hospitals for other reasons during the same period. Some 31 percent of the cases had recently used oral contraceptives, compared with 14 percent of the controls. After adjusting for age, hospital, and year of hospital admission, the relative risk estimate was 3.3, a statistically significant finding. Most of the difference between cases and controls was concentrated in women under age 25. Contrary to what would be expected if the association were causal, duration of use was shorter in cases than in controls (124).

While the researchers noted that oral contraceptives have been linked to gall bladder disease (27) and other changes in liver function, they could not explain an association between OC use and hospital admission for acute hepatitis. One possibility is that some of the cases were pill-related jaundice or some other specific drug reaction that was misdiagnosed (124). Another possibility is that, since hepatitis can be sexually transmitted, it is associated with frequency of coitus and number of partners rather than with OC use directly.

COMPARATIVE RISKS AND BENEFITS

What are the policy implications of both continued oral contraceptive use and continued evidence of health hazards among specific subgroups of women? On the one hand, decision makers are faced with a barrage of press and other news media publicity all too often reporting preliminary research results with little or no reference to or understanding of statistical significance, study design, or different risks for different subgroups of women. On the other hand, the need—and desire—for effective, reversible methods of contraception grows rapidly as both organized family planning programs and the pressures of social and economic change encourage individuals and families to try to control their fertility.

On the government and policy level, those who must decide how to deal with the pressures of burgeoning population and, on the personal level, those who face the threat of unwanted fertility can have no guarantees of absolute safety with or without any method of fertility control. Certainly high fertility and rapid population growth present threats to health and well-being far greater than those of contraceptive methods measured in these medical and epidemiological studies. The most prudent course is to compare, from the medical data available, the relative risks of different family planning methods—including no methods whatsoever—under different conditions of development and to design programs that attempt to provide the maximum benefits consistent with a broad range of choice and cultural acceptability.

Table 26. Annual Number of Birth-Related, Method-Related, and Total Deaths, by Method of Fertility Control, in a Hypothetical Cohort of 100,000 US Women

Regimen	Age in Years					
	15–19	20–24	25–29	30–34	35–39	40–44
No control						
Birth-related	5.3	5.8	7.2	12.7	20.8	21.6
Abortion only						
Method-related	1.0	1.9	2.4	2.3	2.9	1.7
OCs only/nonsmokers						
Birth-related	0.1	0.2	0.2	0.4	0.6	0.4
Method-related	0.6	1.1	1.6	3.0	9.1	17.7
Total deaths	0.7	1.3	1.8	3.4	9.7	18.1
OCs only/smokers						
Birth-related	0.1	0.2	0.2	0.4	0.6	0.4
Method-related	2.1	4.2	6.1	11.8	31.3	60.9
Total deaths	2.2	4.4	6.3	12.2	31.9	61.3
IUDs only						
Birth-related	0.1	0.2	0.2	0.4	0.6	0.4
Method-related	0.8	0.8	1.0	1.0	1.4	1.4
Total deaths	0.9	1.0	1.2	1.4	2.0	1.8
Barrier methods only						
Birth-related	1.1	1.5	1.9	3.3	5.0	4.0
Barrier methods, plus abortion						
Method-related	0.1	0.3	0.4	0.4	0.4	0.2

Source: Tietze and Lewit (199)

To evaluate these risks, C. Tietze, J. Bongaarts, and B. Schearer of the Population Council have designed a computer model that simulates reproductive events during the childbearing years of a hypothetical cohort of 100,000 nonsterile women using various family planning methods (196, 197, 198). Applying the model to developed country data and taking account of the Royal College mortality data and other recent research, Tietze suggests that for developed countries, with low rates of maternal mortality, use of OCs is very much safer than the use of no method at all (with ensuing pregnancies) for nonsmokers under 40 and somewhat safer for smokers under 30. In developed countries, after age 35 the risk of death to OC users who also smoke is about three times greater than normal childbirth and more than three times greater than the risk of OC use to nonsmokers. Tietze's calculations focus attention on the synergistic effects of smoking and OC use in women over 30 in the developed countries, women who may also have other factors predisposing them to vascular disease (see Table 26).

Overall, in developed countries the safest approach for any couple now seems to be using the diaphragm or condom combined with legal abortion in cases of failure and choosing voluntary sterilization after desired family size has been reached. Of course, legal, safe abortion is not available in many countries, and beyond the financial means of some women even where it is legal. Furthermore, many women find traditional methods so difficult or distasteful to use that they prefer orals even if the risk is somewhat greater.

Tietze's methodology has been applied to the developing countries by M. Potts, J.J. Speidel, and E. Kessel (146). They compare mortality rates for different methods and method combinations in moderately developed countries, such as Taiwan and Korea (LDCA), and in the least developed areas, such as Matlab Thana in Bangladesh (LCDB) (see Table 27). In so doing, they make a number of assumptions: for example, that fecundability is the same in developed and developing countries but that an 8-month longer period of lactational amenorrhea follows childbirth in developing countries; that maternal mortality in Korea and Taiwan is representative of rates for middle-income developing countries and, in Bangladesh, for poorer developing countries; that abortion mortality is twice as high in middle-income countries and five times as high in low-income developing countries as in the United States; that use-effectiveness of all methods except IUDs is slightly lower in developing countries; that method-related risks from IUDs and sterilization are two to five times higher in developing countries; and that risks of circulatory disease are lower.

Although Table 26 was prepared before the results of the Royal College study were published, it provides a reasonable comparative guide to the relative hazards of different methods within developed and developing countries. As would be expected, wherever high maternal mortality prevails, the comparative risk of oral contraceptive use is low. For all women in developing countries up to age 40, oral contraceptive use is substantially safer than no use of family planning at all. Even above age 40, in the least developed areas, OCs are safer than pregnancy. Overall, in developing countries as in developed ones, legal abortion

Table 27. Annual Number of Live Births, Birth-Associated Deaths, and Deaths Associated with Fertility Control per 100,000 Nonsterile Women, by Method of Fertility Control, Age, and Development of Country

Method and Outcome	Age Group/Country Type																	
	15–19			20–24			25–29			30–34			35–39			40–44		
	DC	LDCA	LDCB	DC	LDCA	LDCB	DC	LDCA	LDCB	DC	LDCA	LDCB	DC	LDCA	LDCB	DC	LDCA	LDCB
No control																		
Live births	50,770	41,440	41,440	61,400	45,940	45,950	59,290	43,170	43,170	55,730	39,930	39,930	47,700	34,210	34,210	31,680	23,940	23,940
Birth-associated deaths	5.6	8.3	290.0	6.1	9.2	183.8	7.4	10.8	215.9	13.8	20.0	199.7	21.0	34.2	171.0	22.6	35.9	191.5
Abortion																		
Induced abortions	99,502	99,502	99,502	133,664	133,664	133,664	132,041	132,041	132,041	127,278	127,278	127,278	106,209	106,209	106,209	64,779	64,778	64,778
Abortion-associated deaths	1.2	2.4	6.0	1.6	3.2	8.0	1.6	3.2	7.9	2.0	4.0	10.1	1.7	3.4	8.5	1.5	3.0	7.4
Oral contraceptives (without predisposing conditions)																		
Live births	1,150	1,590	1,590	1,940	2,650	2,650	1,910	2,600	2,600	1,770	2,410	2,410	1,350	1,840	1,840	650	890	890
Birth-associated deaths	0.1	0.3	11.1	0.2	0.5	10.6	0.2	0.7	13.0	0.4	1.2	12.0	0.6	1.8	9.2	0.5	1.3	7.1
Method-associated deaths	1.2	0.8	0.8	1.2	0.8	0.8	1.2	0.8	0.8	1.9	1.3	1.3	4.0	3.0	3.0	7.3	5.5	5.5
Total deaths	1.3	1.1	11.9	1.4	1.3	11.4	1.4	1.5	13.8	2.3	2.5	13.3	4.6	4.8	12.2	7.8	6.8	12.6
Oral contraceptives (with predisposing conditions)																		
Method-associated deaths	1.4	1.0	1.0	1.4	1.0	1.0	1.4	1.0	1.0	11.4	6.0	6.0	28.8	13.0	13.0	103.8	63.0	63.0
Total deaths	1.5	1.3	12.1	1.6	1.6	11.6	1.6	1.7	14.0	11.8	7.2	18.0	29.4	14.8	22.2	104.3	64.3	70.1
Intrauterine devices																		
Live births	1,150	1,140	1,140	1,940	1,920	1,920	1,910	1,890	1,890	1,770	1,750	1,750	1,350	1,330	1,330	650	640	640
Birth-associated deaths	0.1	0.2	8.0	0.2	0.4	7.7	0.2	0.5	9.5	0.4	0.9	8.7	0.6	1.3	6.6	0.5	1.0	5.1
Method-associated deaths	0.5	1.0	1.5	0.5	1.0	1.5	0.5	1.0	1.5	0.8	1.5	2.3	1.0	2.0	2.0	1.0	2.0	3.0
Total deaths	0.6	1.2	9.5	0.7	1.4	9.2	0.7	1.5	11.0	1.2	2.4	11.0	1.6	3.3	9.6	1.5	3.0	8.1
Traditional contraception																		
Live births	5,860	7,580	7,580	9,500	11,660	11,660	9,330	11,300	11,300	8,670	10,460	10,460	6,700	8,150	8,150	3,330	4,210	4,210
Birth-associated deaths	0.6	1.5	53.0	0.9	2.3	46.6	1.2	2.8	56.5	2.2	5.2	52.3	2.9	8.1	40.8	2.4	6.3	33.7
Traditional contraception and abortion																		
Induced abortions	7,564	10,273	10,273	11,444	15,483	15,483	11,332	15,317	15,317	10,913	14,764	14,764	8,650	11,721	11,721	4,608	6,271	6,271
Abortion-associated deaths	0.1	0.2	0.6	0.1	0.4	0.9	0.1	0.4	0.9	0.2	0.5	1.2	0.1	0.4	0.9	0.1	0.3	0.7
Tubectomy																		
Live births				0	100	100	0	100	100	0	90	90	0	70	70	0	30	30
Birth-associated deaths				0	0	0.4	0	0	0.5	0	0	0.4	0	0	0.4	0	0	0.2
Method-associated deaths*				0.5	0.9	2.3	0.6	1.2	3.0	0.9	1.7	4.4	2.3	4.6	11.5	13.3	26.7	66.7

DC = Developed Countries; LDCA = Less-developed countries type A; LDCB = Less-developed countries type B
*Mortality during the year of procedure divided by remaining years of fertility

Source: Adapted from Potts et al. (146).

used as a backup for condoms or a diaphragm is safer by an order or more of magnitude than any alternative or combination thereof. Tubectomy mortality, measured as posing a hazard only in the year that the procedure is performed, is in the same range of risk as pregnancy for women over 30 in all but the least developed countries, where it is much less dangerous. For a 35-year-old woman who would gain from tubectomy ten years of protection, the one-time risk of tubectomy spread over ten years may be lower than that of orals. In other words, for the great majority of developing country women under 40, OCs are safer than no method or traditional methods, about as safe as IUDs, and not quite as safe as sterilization or as traditional methods backed by legal abortion performed by trained practitioners.

What these analyses suggest is not that one or another method should be promoted to the exclusion of others—although the increase in safety where legal abortion is available is noteworthy—but rather that different methods may be particularly appropriate for different legal and medical circumstances.

Personal Benefits

The fact remains that despite some plateauing of oral contraceptive use in developed countries, due largely to a worldwide surge of interest in sterilization, especially among older couples, oral contraceptives remain the most popular reversible method of effective contraception. This is a testament to the benefits of the pill—benefits not easily weighed in the balance of medical judgements and epidemiologic studies—and to the fact that, for millions of women, those benefits outweigh the well-publicized but relatively small risks. The late Frederick S. Jaffe, President of the Alan Guttmacher Institute, summarized how individuals benefit from using oral contraceptives and put those benefits in context:

> The pill has two advantages that differentiate it sharply from most other methods:
>
> In the first place, it is the most effective method of preventing pregnancy currently available: as Norman Ryder's studies have shown, IUDs have a standardized 12-month failure rate two times greater than the pill, condoms three times, diaphragms four times and foam, rhythm, and douche more than five times (173).
>
> Secondly, because the pill is coitally independent, it makes possible a greater degree of freedom and spontaneity in sexual relations than methods that need to be applied at the time of intercourse.
>
> No other method meets these basic needs of sexually active persons as well as the pill. These factors suggest that the evaluation framework that has kept the pill in the headlines for the past few years is highly selective and does not reflect adequately the needs and purposes of persons who use contraception. This framework compares medical risks and medical risks alone. Those risks should not be ignored, and accurate information about them should be widely disseminated. But medical risk does not take into account at least two other aspects of the contraceptive experience that users evidently find salient: efficacy in preventing unwanted pregnancy and facilitation of more satisfactory sexual relations. Accurate information about these factors should also be widely disseminated and incorporated into the framework for assessment of risks and benefits.
>
> Implicit in the medical-risk framework is the assumption that other methods of contraception could be substituted, thus rendering the risks from the pill unnecessary. This assumption is true for some persons, but not for all. . . . (87)

Figure 16. To facilitate distribution, three months supply of orals are included in one "Blue Lady" package. Twenty-one pills contain estrogen and progestin, seven pills provide an iron supplement in each of these USAID-supplied packets.

Increasing use of the pill in developing countries suggests that women there, like those in the developed world, appreciate the combination of effectiveness and independence from coitus that oral contraceptives provide. Under the circumstances and conditions many women face in developing countries, these benefits may be very important.

TABLES

Table 12. Various Circulatory System Diseases and Oral Contraceptive Use, Selected Studies, 1967–1977

Author & Date	Ref. No.	Description	Findings
Fuertes-de la Haba et al. 1970	63	Between July 1961 and early 1969, 9,633 Puerto Rican women ages 21–40 were assigned at random to use either OCs (n=4,846) or vaginal contraceptives (n=4,787). Each participant received an annual physical examination and was interviewed every 2 months.	4 deaths not explained by predisposing medical conditions—2 in OC users, 2 in vaginal users. One OC user died 56 days postpartum, diagnosis was congestive heart failure; the other, coronary thrombosis. Both were age 25. One in vaginals group died of pulmonary infarction, one diagnosed as cerebral hemorrhage.

Table 12 (Continued)

Royal College of General Practitioners 1967 — 166

Case-comparison study. OC use in 147 women aged 15–49 diagnosed as having thromboembolic disease, cerebral embolism or thrombosis, subarachnoid hemorrhage or various arteriosclerotic heart diseases between 1961 and 1966 by 29 British general practitioners was compared to OC use in 2 comparison groups selected from same doctors' files.

11.6% of cases were or had been OC users, compared with 5.8% of controls. Venous thromboembolic disease: 16.5% of cases were users, 6.7% of controls. Differences between other disease cases and controls not significant: numbers of cases small. Cases were about 4 times as likely to be pregnant or puerperal as were controls.

Royal College of General Practitioners 1974 — 167

Cohort study conducted in Britain, compares disease occurrence in OC users, nonusers, and those who stopped OC use during study. Study began in 1968 with 23,000 users and 23,000 nonusers, all married and matched for age within 3 years. Total woman-years of observation: users, 34,875; controls, 42,306. Hypertension evaluated according to the customary criteria of participating physicians.

	Rate per 1,000 woman-years (number of cases in parentheses)		
	Users	Controls	Ratio
Acute MI	0.13(5)	0.02(1)	5.22
Angina pectoris	0.21(8)	0.21(8)	1.03
Subarachnoid hemorrhage	0.07(2)	0.02(1)	3.77
Cerebral thrombosis	0.13(4)	0.00(0)	—($p < 0.01$)
Acute but ill-defined cerebrovascular disease	0.16(5)	0.00(0)	—($p < 0.05$)
All cerebrovascular disease	0.41(16)	0.10(4)	4.10($p < 0.01$)
Hypertension	6.62(236)	2.56(105)	2.59($p < 0.01$)

With hypertension, bias likely because users have blood pressure checked more often than do nonusers. Incidence during first year of OC use "probably little higher than the rate to be expected in a comparable population of nonpregnant non-users" but rose with duration of use. Incidence related to age of users and to progestin dose in OCs (see Table 17: Royal College of General Practitioners 1977 (168).

Royal College of General Practitioners 1977 — 169

Cohort study described above. Causes of the 101 deaths that occurred through June 1976 analyzed according to contraceptive status of women. Length of observation in women-years: nonusers—110,065; users and exusers—96,624.

	Death rate per 100,000 woman-years of observation			Ratio of user death rate to nonusers'		
	Current users	Ex-users	Non-users	Ever-user (95% confidence interval)	Current users	Ex-users
All circulatory system disease	26.8	23.9	5.5	4.7* (1.7–14.0)	4.9	4.3
Non-rheumatic heart disease	12.1	7.6	2.6	4.0** (1.3–26.0)	4.7**	3.0
Myocardial infarction	8.1	3.1	2.5	NA	3.2	1.3
Cerebrovascular disease	12.4	14.7	28.	4.7** (1.2–21.4)	4.4	5.3
Subarachnoid hemorrhage	9.3	15.9	0.0	—**	—**	—**
Cerebral thrombosis and hemorrhage	2.6	0.0	2.8	NA	0.9	0.0

*$p < 0.01$ **$p < 0.05$

Rates standardized for age at entry, parity, social class, and smoking. Comparing users and exusers with controls, ratio of rates from all circulatory system diseases, standardized for age, was 3.4 for 1–59 months use, 9.7 for 60 months or more. Also, ratios were 2.0 for ages 25–23, 4.5 for ages 35–44.

Table 12 (Continued)

Vessey et al. 1976	213	Cohort study. Reports rates of hospital admissions and outpatient attendances for 17,032 white, female British family planning clinic clients aged 25–39. 56.6% used OCs at time of entry into study (followed 31,076 woman-years), 24.8% used diaphragms (followed 14,739 woman-years), and 18.6% used IUDs (followed 10,014 woman-years). Rates standardized for age (four groups), parity (parous or nulliparous), social class, and smoking (three groups).	Standardized rates (per 1,000 woman-years) by contraceptive method on admission to study: Disease: Orals / Diaphragms / IUDs All circulatory system disease: 9.80* / 13.36 / 17.27 (Difference due largely to exclusion of women with varicose veins from OC use before entry into study.) Cerebrovascular disease: 0.43** / 0.006 / 0 Venous thrombosis & pulmonary embolism: 0.89 / 0.61 / 0.56 As above, new cases only: 0.86 / 0.38 / 0.32 Hypertension: 1.59 / 1.68 / 0.68 Rates by contraceptive methods used during follow-up; new cases only: Orals / Not orals Cerebrovascular disease: 0.45** / 0.09 Venous thrombosis & pulmonary embolism: 1.06** / 0.33 1.06 / 0.33 10 of 13 were OC users at time of occurrence of cerebrovascular disease. *p<0.001 **p<0.01
Vessey et al. 1977	215	As above (213). Length of observation was: OCs—49,681 woman-years; diaphragms—22,937 woman-years; IUDs—16,209 woman-years. Generally, OC users had fewer risk factors for cardiovascular diseases than did others except that they smoked more.	43 deaths occurred among study participants, 9 from cardiovascular disease. All 9 were OC users (includes 12 deaths of women deleted from study and not included in rate calculations). Rates for OC users, standardized for age, parity, social class, and smoking: All circulatory disorders: 13.6* Non-rheumatic heart disease: 9.8 Cerebrovascular disease: 3.8 *Significantly different from rates of 0.0 in diaphragm and in IUD users (p<0.05). 5 of the 9 women dying from cardiovascular disease smoked 15 to 20 cigarettes per day.

Table 15. Venous Thromboembolism, Stroke, and Oral Contraceptive Use, Selected Studies, 1968–1978

Author & Date	Ref. No.	Description	Findings
Badaracco & Vessey 1974	13	76 women with previous diagnosis of **deep vein thrombosis or pulmonary embolism** without evident predisposing cause were asked about recurrences of thromboembolic disorders. About half had been using OCs within 1 month of previous diagnosis. Subsequent use of OCs negligible.	Proportion free of recurrences unrelated to childbearing Former Users / Nonusers After 3 years: 92% / 64% After 6 years: 86% / 57% 3 former users and 3 nonusers had recurrences related to childbearing.
Collaborative Group for the Study of Stroke in Young Women 1973 & 1975	40, 41	Case-comparison study. OC use in 429 women with **cerebrovascular diseases**, admitted to 91 hospitals in 12 US cities in a 2-year period and who could be interviewed, compared with that in women from the same hospitals (n=393) and from cases' neighborhoods (n=450), matched for age by decade and race.	Overall, and in each 10-year age group, almost twice as many cases as controls were current users of OCs. Relative risk was higher in whites than in blacks. Relative risk estimates, based on matched pairs: Hospital Controls / Neighborhood Controls Thrombotic stroke: 9.5 / 8.8 Hemorrhagic stroke: 2.0 / 2.3 Other strokes: 1.1 / 1.0

Table 15 (Continued)

			Smoking alone significantly increased risk of hemorrhagic stroke but not of thrombotic stroke. OC use and smoking had synergistic effect on occurrence of hemorrhagic stroke. Risk of stroke associated with OC use not synergistic with risk associated with hypertension.
Fuertes-de la Haba et al. 1971	64	Between July 1961 and May 1969, 9,898 Puerto Rican women aged 21–40 were assigned at random to use either OCs (n=4,965) or vaginal contraceptives (n=4,933). Each participant received an annual physical examination and was interviewed every 2 months. As of June 1969, 87% were still being followed.	17 first occurrences of nonpuerperal **thrombophlebitis** not associated with other conditions were reported, 9 in the OC group, 8 in the vaginal contraceptive group. Incidence rates: 1.8/1,000 in OC group; 1.6/1,000 in vaginal contraceptive group. Not a statistically significant difference. No significant differences found after adjustment for several variables nor in probabilities of developing thrombophlebitis during the study's 8-year period (4.5/1,000 in the OC group; 4.0/1,000 in the vaginal contraceptive group).
Greene & Sartwell 1972	71	Case-comparison study. OC use compared in 60 cases of **thromboembolic disease** developing after hospital admission for surgery, trauma, systemic infection, or immobilization, and in one or two controls each (n=98), all admitted to hospitals for reasons similar to those of cases, matched to cases by race (all Caucasian), marital status, age within 10 years, and date of hospital discharge within one year.	35% of cases and 16.7% of controls had used OCs within 1 month of hospital admission. In 13 case-control pairs, only case had used OCs; in two, only the control. Relative risk estimate: 6.5 ($p=0.007$). No difference in duration of use between case-users and control-users. Risk appeared to cease when OC use stopped.
Hoover et al. 1978	79	65,843 women from the Boston (USA) area answered a 1970 questionnaire about lifetime OC use and 1969 hospitalizations. Rates of hospitalization of ever-users and non-users compared.	Annual rate of hospitalization for **thromboembolism** per 1,000 women: users: 2.0; nonusers: 1.3 ($p=0.06$); relative risk: 1.5. Age 25–29; users: 2.0; nonusers: 0.4 ($p<0.05$); relative risk: 5.0. (Young age group most likely to be free of factors predisposing to thromboembolism, which might obscure effect of OCs.) Rate of hospitalization did not increase with duration of use. OC users hospitalized 20–40% more frequently than nonusers, whether or not condition associated with OC use.
Inman & Vessey 1968	83	Case-comparison study. 309 deaths due to **thrombosis** or **embolism** (99 pulmonary, 209 coronary or myocardial infraction, 30 cerebral) that occurred in 1966 in married, nonpregnant women aged 20–44 in England, Wales, and Northern Ireland were examined via interviews with doctors. OC use in these women was compared with use in 998 women whose records were drawn from the files of cases' doctors. Two groups of cases: Class A—without known predisposing conditions; Class B—with known predisposing causes.	Pulmonary embolism: Class A—16 or 26 cases had been using OCs at time of death, compared with 4.2 expected based on controls of like parity and age ($p<0.001$); Class B—9 of 49 in whom contraceptive practice known were OC users, compared with 6.8 expected. Coronary thrombosis: Class A—18 of 84 in whom contracptive practice was known were OC users, compared with 11.4 expected; Class B—5 of 110 of known contraceptive status had been OC users, compared with 12.6 expected. Cerebral thrombosis: Class A—5 of 10 were OC users, compared with 1.5 expected ($p<0.01$); Class B—none of 16 of known contraceptive status was an OC user.
Inman et al. 1970	84	The distribution, types, and doses of OCs used by women in 1,024 cases of **thromboembolism** in OC users reported to the Committee on Safety of Drugs (UK) between January 1965 and June 1969 were compared to expected distribution based on sales data.	Of 920 reports from the UK involving combined OCs, high estrogen doses more frequent than expected, especially for pulmonary embolism, cerebral thrombosis, and coronary thrombosis. No consistent differences seen between reported and expected cases according to type of regimen (sequential or combined).
Jick et al. 1978	95	Case-comparison study. OC use by 14 premenopausal women without factors predisposing to **stroke** and without contraindications to OC use, admitted with diagnoses of stroke to 21 hospitals in 7 countries since 1969 or to 24 Boston (USA) area hospitals in 1972, was compared with OC use by four controls for each case, matched for country, age (±4 years), and criteria for inclusion of cases. Most of strokes were thrombotic, not hemorrhagic.	11 of 14 cases (79%) had used OCs just before admission, compared with 7 of 56 controls (13%). Risk did not appear to change with age, and smoking only weakly associated with risk of stroke. Relative risk estimate: 26:1. "Although the current results indicate that oral contraceptives markedly increase the risk of stroke in healthy young women, it is worth emphasizing that the illness is rare in this population."

Table 15 (Continued)

Petitti & Wingerd 1978 — 144

Case-comparison study. In the Walnut Creek Contraceptive Drug Study, 11 of 16,759 participants developed **subarachnoid hemorrhage**. Each case was matched with all women from study of same age (total, 3,956 controls; range 197–516 per case). Of the cases, 9 were or had been OC users, 8 were smokers at entry to study.

	Percentage		Relative risk
	Cases	Controls	
Current users of OCs	36.4	10*	6.5
Smokers at entry to study	72.7	33*	5.7
Current OC users and smokers at entry	36.4	3.2**	21.9
Past users of OCs	71.4	35.6*	5.3

*p < 0.05 **p < 0.001

"Because of the small number of cases it is not possible to determine the magnitude of risk associated with current or past OC use separately for non-smokers. . . ."

Petitti et al. 1978 — 145

Case-comparison study of 38 cases of **thromboembolic disease** without immediate predisposing factors and, as controls, women of the same age as each case (total of 8,174 controls), all from the Walnut Creek Contraceptive Drug Study. 17 cases occurred in the absence of hypertension, diabetes, varicose veins, or history of thromboembolism.

Cases without other risk factors (n=17) and controls:

Percentage OC users		Relative risk estimate
Cases	Controls	
53	19	7.7

No interaction of tobacco and OC use observed, although smoking was an independent risk factor. In all 38 cases and their controls, OC use was twice as frequent in cases, not a statistically significant difference. Hypertension, diabetes, varicose veins, and previous thromboembolic disease also risk factors for venous thromboembolism.

Royal College of General Practitioners 1978 — 170

Cohort study of British OC users, nonusers, and former users, begun in 1968, collecting records of their physicians' diagnoses of illness. Considers only cases without predisposing factors. Periods of observation: users: 34,482 woman-years; former users: 14,769; nonusers: 47,084.

Rate per 1,000 woman-years (number of cases)			Ratio of rates	
Users	Ex-users	Nonusers	Users/ nonusers	Ex-users/ nonusers
Deep vein thrombosis of leg				
0.82 (30)	0.15 (2)	0.20 (9)	4.17*	0.75
Superficial vein thrombosis of leg				
1.86 (67)	0.87 (12)	0.77 (36)	2.41**	1.13

*p < 0.01; 95% confidence interval: 2.1–10.9
**p < 0.01; 95% confidence interval: 1.4–12.7

No relationship with smoking observed.

Rates per 1,000 woman-years (no. of cases) among women using OCs consisting of ethinyl estradiol 50 μg + norethisterone acetate in varying amounts:

	1 mg	3 mg	4 mg
Deep vein thrombosis of leg	0.78(5)	0.91(7)	0.0(0)
Superficial vein thrombosis of leg	0.63(4)	2.09(16)	2.25(3)

Sartwell et al. 1969 — 177

Case-comparison study. OC use in 175 women aged 15–44 discharged from 43 US hospitals after diagnosis of **thrombophlebitis**, **pulmonary embolism**, **cerebral thrombosis of embolism** without evident predisposing conditions or events was compared with OC use in 175 women discharged from same hospitals within 6 months of cases and individually matched for age within 5 years, residence, race, parity, and hospital pay status. Those infertile or with chronic diseases were excluded from study.

67 cases and 23 controls had used OCs within 1 month of hospitalization. 67 cases and 23 controls had stopped using OCs earlier. Duration of use did not affect risk. In 57 case-control pairs, only the case had used OCs within one month of hospitalization; in 13, only the control had used OCs. Estimated relative risk: 4.4 (p < 0.001).

Table 15 (Continued)

Stolley et al. 1975	192	Case-comparison study involving 461 women ages 15–49 with **thromboembolic disease** except cerebrovascular accidents who were admitted to 37 US hospitals, 1970–73. 1,302 controls selected from women admitted to the same hospitals within 14 months of cases and matched for race, age (three groups), and marital status. 104 cases were classified "idiopathic," i.e., without history or evidence of previous thrombosis, predisposing disease, or recent surgery or trauma. These women were considered separately, since the others might have been advised against using OCs.		% using OCs within one month of hospital admission	
				Cases	Controls	Relative risk†
			All cases	30.2	18.7	1.9*(2.1)
			"Idiopathic" cases	56.7	18.8	7.2*(6.1)
			*$p < 0.001$ †Relative risk estimates after adjustment for other relevant differences between cases and controls are shown in parentheses. Relative risks slightly higher for those using OCs containing 100 μ g estrogen or more than for those using less estrogen.			
Vessey & Doll 1968	211	Case-comparison study. OC use in 58 married women under age 40, admitted to 19 British hospitals, 1964–1966, for **deep vein thrombosis or pulmonary embolism** without evident predisposing factors, compared with OC use in two women selected for each case, in hospital for acute medical or surgical condition or for elective operation and matched for hospital, date of admission (±four months), age (±four years), parity, and the criteria for acceptance of the cases. Cases of cerebral thrombosis and coronary thrombosis also examined and compared with controls selected for thrombosis and pulmonary embolism cases.	45% of cases used OCs within 1 month of occurrence of the disease, 9% of controls ($p < 0.001$). Nonuser cases had more frequently had previous thromboembolic attacks than had users, but difference in OC use was significant among those without previous attacks ($p < 0.001$). Cases were heavier smokers than controls, but difference "statistically not quite significant." Among cerebral thrombosis cases, 5 of 9 had used OCs within one month of illness; among coronary thrombosis cases, none of 13.			
Vessey & Doll 1969	212	As above (211), with the addition of 26 more cases of **venous thromboembolism**, all diagnosed in 1967, and two controls each. Also, 10 additional cerebral thrombosis cases and 4 coronary thrombosis cases were considered.	Of the 1967 cases, 62% used OCs; of the controls, 25% ($p < 0.001$). Of a total of 19 cases of cerebral thrombosis, 11 were users. Based on controls for venous thromboembolism cases, adjusting for age, parity, and year of hospital admission, expected number was 3.5 ($p < 0.001$). Coronary thrombosis: 2 of 17 cases had been OC users; expected, 2.1.			

Note: See also Table 12: Vessey et al. 1976 (213); Vessey et al. 1977 (215).

Table 16. Myocardial Infarction (MI) and Oral Contraceptive Use, Selected Studies, 1967–1978

Author & Date	Ref. No.	Description	Findings
Arthes & Masi 1976	11	Case-comparison study. OC use in 136 women aged 30–44 diagnosed in 47 US hospitals as having myocardial infarction compared with that in: 354 women aged 30–44., patients at same hospitals, selected as controls for a study of thromboembolic disease.	Among the 65 menstruating cases, 8 used OCs; 4.7 expected. Difference statistically significant ($p < 0.02$) for 35–39 age group (5 users in 15 cases, 2 in 34 controls). Cases significantly more likely than expected to be smokers.
Bengtsson et al. 1973	20	Case-comparison study. OC use in 29 women with agina pectoris and 23 with "coronary ECG" found in a population survey of women aged 38, 46, 50, 54, and 60 in Göteborg, Sweden, and in 47 Göteborg-born women who had been hospitalized for heart attacks, 1968–70, compared with OC use in all 1,462 women interviewed in the population survey.	12% of women aged 38 in the population study were current OC users and another 12% had been users. None of the cases had ever used OCs.

Table 16 (Continued)

Jick et al. 1978	94	Case-comparison study. OC use in 26 women under age 46, admitted to various US hospitals in the first half of 1975 for nonfatal MI, all of them potential OC users without medical conditions predisposing to MI, was compared with OC use in 59 controls, matched to cases for hospital and time of admission, all of them potential OC users without contraindications to use.	Cases OCs, regardless of smoking Smoking, regardless of OC use Smoking, OCs OCs, no smoking Smoking, no OCs Estimate of risk associated with OC use: 14:1; associated with smoking >25 cigarettes per day: 34:1. ". . . acute MI in otherwise healthy premenopausal women is almost exclusively an illness of cigarette smokers. Therefore, we estimate that among nonsmokers the risk of nonfatal MI attributable to oral contraceptives . . . is extremely small."
Mann et al. 1975	118	Case-comparison study. OC use in 58 living women under age 45 with diagnosis of myocardial infarction compared with that in 166 controls, from same English and Welsh hospitals, matched for marital status, 5-year age group, and year of admission to hospitals.	29.3% of cases had used OCs within a month of heart attack, compared with 8.4% of controls. Relative risk: 4.5 ($p < 0.001$). After accounting for tobacco use, relative risk: 3.2 (Independent of OC use, relative risk of smoking 15 to 24 cigarettes a day was 4.1 times that for nonsmokers; 25 or more cigarettes a day, 11.3.)
Mann et al. 1975	117	As above (118), but involving 14 cases and their controls (n=24) from another region of England.	3 cases (21.4%) and 2 controls (8.3%) had used OCs within one month of admission to hospital. When data from all regions were combined, 27.8% of 72 cases and 8.4% of 190 controls were "current" users. Risk ratio: 4.2 ($p < .001$); after standardization for cigarette smoking and other risk factors for MI: 3.1 ($p < 0.05$). "No appreciable difference" in proportions of ex-users among cases and controls.
Mann & Inman 1975	115	Case-comparison study. All deaths from myocardial infarction in England and Wales, 1973, of women under age 40, half those of women ages 44–44, and 1 in 5 of those of women 45–49 on which information could be obtained—a total of 153—were examined. Comparison group was living women, 1 or 2 matched to each case by five-year age group and marital status, chosen from files of the cases' doctors.	Percentage Using OCs Age / Cases / Controls / Relative Risk 40 / 44.7 / 22.4 / 2.8 ($p < 0.02$) 40–44 / 15.4 / 3.8 / 4.7 ($p < 0.05$)* All / 21.4 / 10.5 / NR Average use longer among cases than among controls. Proportions of ex-users among cases and controls similar. Use of high dose estrogen products before 1970 was not more common among cases. *See Mann et al. 1976 (116), below.
Mann et al. 1976	116	As above (115), including 54 more deaths due to myocardial infarction in the 40–44 age group, for a total of 106, and 50 more controls.	Based on larger numbers, relative risk of fatal MI in OC users ages 40–44 compared to nonusers of same age: 2.8. After adjustment for differences in other risk factors (not including smoking): 2.7.
Rosenberg et al. 1976	159	Case-comparison study. Use of oral contraceptives and other estrogen-containing products was compared in 34 women with nonfatal MI and in 1,213 women admitted for other reasons, excluding reasons which might be associated with use of estrogens, to 45 hospitals in 7 countries, 24 of the 45 in the area of Boston (USA). Study participants were all premenopausal women who could be interviewed.	Of 34 with nonfatal MI, 4 (11.8%) used OCs and 2 (5.9%) used other estrogen-containing products. In the comparison group of 1,213, use was 6.5% and 2.1%, respectively. Crude rate ratio for OCs: 1.9; standardized for age, cigarette smoking, and other risk factors: 1.3; crude rate ratio for other estrogen products: 2.8; standardized: 2.1. Differences not statistically significant.
Rosenberg et al. 1977	160	Case-comparison study. OC use in 159 cases of premenopausal MI leading to hospitalization compared with that in 3,180 controls. All participants were married female nurses in US states.	13% of cases were current users of OCs, compared with 8.6% of controls. After adjustment for other relevant variables, including cigarette smoking, risk for current users relative to never users was 1.8 (95% confidence interval: 1.1 to 3.0).

Note: See also Table 15: Inman & Vessey 1968 (83).

Table 17. Hypertension and Oral Contraceptive Use, Selected Studies, 1969–1978

Author & Date	Ref. No.	Description	Findings
Clezy et al.	39	77 Australian women aged 17–40 had blood pressure checked before and, at approximately 3-month intervals, for 3 months to 2 years after 74 started using OCs. Hypertension defined as blood pressure of 150/90 mm Hg or higher.	Mean systolic pressure significantly higher during OC use. Of 240 readings before OC use, percentage hypertensive: systolic—1.29; diastolic—6.49; both—0. During use: diastolic —28.4; systolic—23.0; both—23.0. Six developed sustained systolic hypertension, including 3 who also developed sustained diastolic hypertension and experienced symptoms. Incidence of hypertension higher in those with history of hypertension in pregnancy or with familial history than in those without such backgrounds. Hypertension likely to develop soon after starting OC use.
Fisch & Frank 1977	58	Cohort study, at the Kaiser-Permanente Medical Care Program, Walnut Creek, California (USA). 9,511 women were examined 2 or more times; 3,847 only once. 4,088 were OC users at time of examination; 4,609 were past users; 4,661, never users. Elevated blood pressure defined as over 140/90 mm Hg.	Age-adjusted proportion with elevated blood pressure lower for past users than for never users, significantly higher for current users (4%) than for past or never users (1.5%). Women over age 35 accounted for the difference. Dose, duration of use, and chemical composition of OCs unrelated to blood pressure change. OC use did not interact with alcohol consumption, age, family or personal history of hypertension, or relative weight. For those examined twice, mean change in blood pressure was not significant either for those not using OCs at both exams nor for those using OCs at both exams. Significant decrease in those who had stopped using OCs between exams. Increases of roughly equal magnitude for all women can be inferred.
Greenblatt & Koch-Weser 1974	69	Case-comparison study. Blood pressure readings taken for 921 women aged 20–44, admitted to 24 Boston area hospitals for acute illness or elective surgery in 10 months of 1972, who were free of chronic disease, histories of hypertension, diabetes, myocardial infarction, and other diseases possibly related to or contraindicating OC use. Hypertensive blood pressure defined as 140/90 mm Hg or higher.	289 (31.4%) hypertensive. 63 (21.8%) used OCs, compared with 125 (19.8%) of normotensives. Age-standardized risk ratio: 1.47 ($p < 0.05$). In 4 of 5 five-year age groups, OC use was more prevalent among hypertensives. Mean blood pressures were higher in users than in nonusers, but differences were not statistically significant.
Hoover et al. 1978	79	Cohort study. 65,843 women from the Boston (USA) area answered a 1970 questionnaire about lifetime OC use and 1969 hospitalizations. Rates of hospitalization of ever-users and nonusers compared.	Annual hospitalization rate per 1,000 women: users: 1.0; nonusers: 0.3 ($p < 0.05$); risk ratio: 3.3. Rate of hospitalization increased with duration of use. OC users hospitalized 20–40% more frequently than nonusers, whether or not for conditions associated with OC use.
Kunin et al. 1969	106	Blood pressure readings were taken for 2,302 working white women aged 15–44 in Virginia (USA). 496 (31.5%) were OC users. Mean blood pressures, adjusted for age, height, weight, and arm circumference, compared between OC users and nonusers. Also compared were readings taken in 517 study participants a year after the first readings.	Mean adjusted blood pressure at first reading slightly higher in OC users—2.3 mm Hg systolic, 1.2 mm Hg diastolic (p 0.05). In those who used OCs at both examinations diastolic pressure only rose, but not significantly in those who were nonusers at both exams. No significant changes in mean blood pressure in the few changing contraceptive status between exams.
Pritchard & Pritchard 1977	147	Blood pressure measurements before and during OC use were taken for 180 primiparous US women. 26 of these had had eclampsia or overt pregnancy-induced hypertension. Also recorded were blood pressure measurements for 200 young nulliparous women using an OC for the first time. All participants used the same OC (norethindrone 1 mg + mestranol 50 μg).	9 (5.8%) of the primiparas developed diastolic pressures over 90 mm in the 3-year follow-up period, 5 within 3 months after starting OCs. Pressure remained high in 5 after they stopped OC use, implying underlying chronic hypertension. None of 26 who had eclampsia developed hypertension while using OCs. 5 of 200 (2.5%) nulliparas developed diastolic pressures of >90 mm. Mean systolic and diastolic pressures did not change markedly for any group. "The frequency and the intensity of the hypertension identified in this study do not appear sufficiently great to preclude the use of oral contraception by all women who suffered pregnancy-induced hypertension during their first pregnancies."

Table 17 (Continued)

Ramcharan et al. 1974	149	Walnut Creek cohort study. Comparing prevalence at time of entry and subsequent occurrence of diseases in 11,672 women, aged 20–54. At entry into the study between December 1968 and December 1971, 3,569 had never used OCs, 3,851 were current users, 4,252, former users. Average period of observation was over 19 months for all three groups. Hypertension defined according to individual criteria of 30 participating internists.	Prevalence of hypertension at entry into study age-adjusted: current users, 13.9/1,000; never users, 7.8/1,000 ($p < 0.05$); past users, 6.7/1,000. Higher rates for users than never users in all 5-year age groups except < 25 group. Incidence in users relative to that in never users increased with age. Rates of occurrence of hypertension during study, age-adjusted: current users, 6.2/1,000; never users, 0.9/1,000 ($p < 0.001$); past users, 1.1/1,000.
Ramcharan et al. 1977	150	Walnut Creek cohort study. Incidence of labile and essential hypertension in 14,089 white women aged 20–54 who, at entry into study between December 1968 and February 1972, were free of hypertension. Average follow-up: OC users at entry (n=3,815): 39.9 months; past users (n=4.441), 37.5; never users (n=4,479), 41.0. High blood pressure defined as 140/90 mm Hg. 1,354 women using estrogen hormones were studied separately, regardless of OC use status.	Age-adjusted rates per 1,000 woman-years: Hormone use at entry into study Hypertension: Never; OCs, Past; OCs, Current; Estrogen Essential: 4.1; 4.5; 4.8; 5.1 Essential & labile: 7.1; 7.3; 10.3; 11.0 Estimated risks relative to never users, standardized for weight, parity, parental history of hypertension, and utilization of medical services: Past Users / Current Users Essential: 1.12 / 1.31 Essential & labile: 1.06 / 1.57* *($p < 0.01$) Duration of use had no clear effect on incidence rates or relative risk. Ratio of rates (users/never users) did not rise consistently with age. Relative risk may be underestimated due to changes of contraceptive method after entry and exclusion of those with labile hypertension at entry. "Actual increase in risk [may lie] somewhere between two and sixfold."
Ravenholt et al. 1977	153	Blood pressure readings were taken for 480 women who had not used OCs within preceding 3 months. Readings taken again after 3 cycles of OC use. 155 used Ovral® (norgestrel 0.5 mg + ethinyl estradiol (EE) 0.05 mg); 149, Norinyl® (norethindrone 1.0 mg + mestranol 0.05 mg); 154, Norlestrin® (norethindrone acetate 1.0 mg + EE 0.05 mg).	Mean blood pressure readings (systolic/diastolic): Before Use / After 3 Cycles Ovral: 114.9/70.5 / 111.8/68.3 Norinyl: 115.0/71.1 / 110.6/68.8 Norlestrin: 116.9/70.6 / 113.3/68.7
Royal College of General Practitioners 1977	168	Among OC users in the Royal College study were groups using three products, each with the same quantity of the same estrogen, but with varying quantities of the same progestin, norethisterone acetate. Occurrence of hypertension associated with the three products was compared.	Progestin dose / Woman-years of observation / Incidence per 1,000 woman-years 1 mg: 10,866: 8.19 3 mg: 13,821: 12.30 4 mg: 2,522: 13.88 Trend is statistically significant ($p < 0.005$).
Weir et al. 1975	220	Cohort study, Glascow, Scotland (UK). Blood pressure changes over time were recorded for 235 users of oral contraceptives, 249 followed for 2–5 years, and compared with readings in 111 users of diaphragms or IUDs. Hypertension defined as pressure of 140/90 mm Hg or higher.	8 OC users showed hypertensive systolic readings; 2, hypertensive diastolic readings. No apparent clinical complications associated with blood pressure changes. Mean systolic and diastolic pressures rose significantly in users, particularly in first two years of use. No significant changes seen in controls.

Note: See also Table 12: Royal College of General Practitioners 1974 (167); Vessey et al. 1976 (213).

Table 18. Comparison of Vital Statistics Trends and OC Use, Selected Studies, 1968–1978

Author & Date	Ref. No.	Area	Rates Compared	Findings and Conclusions
Anderson 1970	6	Ontario, Canada	Changes between average rates for 1959–61 and for 1966–68 in females aged 15–44 compared with changes for males aged 15–44.	Percentage change: Females / Males **All circulatory system diseases**: –11 / –10 **Venous thromboembolism**: +200 / +25 **Cerebral thrombosis**: +58 / +17 **Arteriosclerotic and other degenerative heart disease**: +2 / –8
Belsey et al. 1978	19	Same as Beral 1976 (21) (see below)	For 3 ten-year age groups 15–44, period between 1955 and year of 1/3 peak OC use compared with years of peak use thereafter.	**Circulatory system disease**—11 trends were statistically significant: 4 adverse trends associated with growing OC usage in 15–24 and 25–34 age groups, 7 improvements in 35–44 age group. Countries with significant adverse trends had OC use rates below median for all countries.
Beral 1976	21	21 countries (16 European countries, USA, Canada, Australia, New Zealand, Japan)	For females aged 15–44, 1955–56 compared with 1961–62 and 1961–62 compared with 1971–72. For females aged 45–64 and for males aged 15–44, 1961–62 compared with 1971–72.	**All non-rheumatic cardiovascular disease, non-rheumatic heart disease and hypertension, and cerebrovascular disease**—mortality rate changes for women aged 15–44 generally correlated with the proportion of women estimated to be using OCs during the latter period, with largest percentage increase in rates taking place in areas with the highest proportion of OC users. Similar correlations were not observed for young women between 1955–56 and 1961–62, older women, or men. Trends in individual countries are not identified. Changes in per capita cigarette consumption were not correlated with changes in mortality rates nor with proportion using OCs.
Chow 1978	34	Taiwan	Females and males aged 20–49 in 5-year age groups, 1965–1976.	**Cerebrovascular disease**—No trends in disease mortality rates correlated significantly with trends in estimated OC use. Slight declines in rates in women after 1968, perhaps due to reduced fertility. No comparable declines in rates for men. "The fact that the mortality rates from stroke among childbearing age women had not shown any significant upward trend after introduction of the oral contraceptive in 1967 is encouraging, suggesting, although not proving, that the pill probably had not had an overwhelming adverse effect on stroke mortality."
Frederiksen & Ravenholt 1970	62	USA	Females and males aged 20 and older in several age groups. Percentage increase between 1956–61 and between 1961–77 compared.	**Thromboembolic disease**—percent increase in mortality: 1956–61: Men / Women; 1961–66: Men / Women 20–34: 48 / 40 / 22 / 77 35–44: 6 / 17 / 65 / 134 20–44: 20 / 28 / 47 / 105 44+: 60 / 74 / 42 / 49 "It may be significant that, with the exception of the group 20–44 years of age, the increase was about the same for all age groups and for both sexes. In women in the age group 20–44 years, however, mortality due to thromboembolism increased more than twice as much as for men from 1961 to 1966, after oral contraceptives came into use." If the difference in rates is assumed to be due solely to OCs, "the excess mortality due to thromboembolism per annum is estimated at 3.6 deaths per 100,000 users of oral contraceptives 20–44 years of age."
Gram et al. 1976	68	Denmark	Females aged 15–49, 1955–72.	**Thrombophlebitis, pulmonary infarction, and cerebral infarction** combined—5-year moving average of number of deaths (not death rates) declined from about 15 per year in late 1950s to 11 per year in early 1960s, then rose. Rise moderated slightly after the introduction of OCs. "The introduction of [OCs] in Denmark in 1966 had no significant influence on the incidence of deaths from thromboembolic disease. . . ."

Table 18 (Continued)

Greene 1969	70	USA	Females aged 15–65, in 10-year age groups, compared with males, 1956–66.	**Intracerebral hemorrhage**—rates declined in both sexes, but in 1965–66 rate for females aged 25–34 was higher than that for males for first time. **Subarachnoid hemorrhage**—rates rose steadily and steeply in both sexes, but faster in females, except for the 15–24 year age group. "No explanation of this finding is readily available." **Cerebral embolism and thrombosis**—no definite trends in two lower age groups due to small numbers. Rates were stable for both sexes in three higher age groups. "An analysis of these data does not warrant any conclusions regarding the influence of [OCs] on cerebrovascular mortality."
Markush & Seigel 1969; **Seigel & Markush 1969**	119 181	USA USA	Females aged 15–64 in 5-year age groups. Trends for 1956–61 compared with those for 1962–66. Whites and other races analyzed separately. Changes in trends for females compared with those for males.	Data support hypothesis linking OCs and **diseases of veins**, but not OCs and **cerebral embolism and thrombosis** or **arteriosclerotic heart disease**. Estimating risk of death from diseases of veins for OC users relative to nonusers, 3–9.
Oliver 1974	134	England & Wales	Females aged 35–65, in 10-year age groups, 1950–70.	**Ischemic heart disease**—rates for all three age groups declined at the same increasing pace during the early 1950s. About 1958 the rate of decline became constant for all groups. By the early 1960s, rates for the 35–44 year age group began to rise at an increasing pace; betwen 1958 and 1970, the death rate rose more than 50%. Rates for the 45–54 year age group began rising in the mid-1960s. Declines in rate continued at a fairly steady pace in 55–64 year age group during the 1960s. Increased rate among young women "unexplained," but possibly due to more cigarette smoking.
Sartwell & Anello 1969	176	USA	White females aged 15–64, in 10-year age groups. Trends for 1956–61 compared with those for 1962–66. Changes in trends for females compared with those for males.	Data support hypothesis linking OCs and **venous thromboembolic diseases**, although some age groups show contrary trends. For **pulmonary embolism**, increases in rates were greater for females than for males in all but youngest age group, but differences were not statistically significant, perhaps due, in younger age groups, to small numbers.
Sartwell et al. 1976	178	USA	Females aged 15–54, in 10 year age groups, for periods 1961–63, 1964–66, 1967–69, and 1970–72, compared with those for males. Whites and other races examined separately.	**Pulmonary embolism**—in 15–24 and 25–34 year age groups, ratio of female to male rates rose sharply during 1964–66, then declined. No such pattern in the 35–44 year age group. In the 45–54 year age group, rates in females were slightly less than those in males. Findings "consistent with the view that OCs have somewhat increased female mortality from this condition." Fall in ratio for younger age groups after 1966 may be due to reduced estrogen dose in OCs or growing acceptance of predispositions to venous thromboembolism as contraindications to OC use.
Vessey & Weatherall 1968	216	England & Wales	Females aged 20–34 and 35–64, in 10-year age groups for 1953–67, compared with males.	**Thromboembolic disease**—rates for both sexes in 20–34 and 35–44 year age groups rose after 1962, but more quickly for females. In older age groups, rates for both sexes rose steadily, except for females aged 55–64, for whom increases slowed slightly after 1962. Trends compatible with hypothesis of link between OCs and thromboembolic disease.
Vessey & Inman 1973	214	England & Wales	As above (216), through 1971.	Trends compatible with hypothesis linking OC use and **thromboembolic disease**, but no evidence that rapid reduction in estrogen dose and lag in growth of OC use in 1970 lowered death rates.

Table 24. Birth Defects and Oral Contraceptive Use, Selected Cohort Studies, 1976–1978

Author & Date	Ref. No.	Study	No. of Births studied: Non-users	Users before pregnancy	Users during pregnancy	Births defects studied	% of births: Non-users	Former users	Users during pregnancy	Comment
Harlap & Davies 1978	73	Jerusalem Perinatal Study	13,630[a]	— 2,953 —	108	All malformations	7.66[a]	7.35	9.26	Pill users generally healthier than nonusers. Significantly high rates of Down's syndrome only in offspring of pill users of Asian origin ($p<0.05$) or of less than average weight-for-height ($p<0.01$). Users over age 35 at more risk than nonusers for Down's syndrome and other major malformations.
						Down's syndrome	0.18	0.33	0.92	
						Heart defects	0.40	0.20		
						Limb reduction	0.01	0.03		
						Neural tube defects	0.25	0.20	0.92	
Heinonen et al. 1977	75	Collaborative Perinatal Study	— 49,240 —		218	Cardiovascular defects	— 0.78 —		2.15	Adjusted relative risk: 2.4 (not statistically significant). However, there were 1.82% cardiovascular defects in 1,042 infants exposed in uterus to estrogen, progestin, or both, including OCs; relative risk: 2.3 ($p<0.05$).
Rothman & Louik 1978	164	Boston area survey	2,188[b]	3,087[c]	1,448[d]	All malformations	3.3[b]	3.6[c]	4.3[d]	No specific malformation showed association with OC use.
						Major malformations	0.55[b]	—	0.55[d]	
Royal College of General Practitioners 1976	171	Royal College	9,511	4,477	102	All congenital malformations	1.84	1.90	1.96	No specific malformation showed association with OC use.
			Special inquiry to physicians:				Special inquiry to physicians:			
			1,000	1,000	—		3.38	3.31	—	
Vessey et al. 1976	213	Oxford/FPA study	Nulliparous, planned[e]:			All congenital malformations				"While our overall findings are reassuring . . ., we have as yet accumulated information about too few cases of each of the major types of malformations for individual examination."
			282/1	653	—		0.4/—[f]	3.8	—	
			Parous, planned[e]:							
			429/121[f]	484	—		4.0/2.5[f]	2.3	—	
			Nulliparous, unplanned[e]:							
			27/—	—	2		3.7/—[f]	—	—	
			Parous, planned[e]:							
			166/115	—	22		1.8/0.9[f]	—	4.5	Only case of limb reduction defects was child of former diaphragm user.

[a] No OC use since previous pregnancy
[b] No OC use within 3 years of conception
[c] OC use 1–12 months before conception
[d] OC use within one month of conception
[e] Singleton pregnancies only
[f] Ex-diaphragm/ex-IUD

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Erratum

In **Population Reports** J-20, "Filling Family Planning Gaps" (September 1978), the authors' names in references 71–73 were inadvertantly transposed. Corrected, the references read:

ZELNIK, M. and KANTNER, J.F., Contraceptive patterns and pregnancy among women aged 15–19 in 1976. Family Planning Perspectives 10(3): 135–142. May–June 1978.

ZELNIK, M. and KANTNER, J.F., First pregnancies to women aged 15–19: 1976 and 1971. Family Planning Perspectives 10(1): 11–20. January–February 1978.

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